

**The London School of Economics and Political Science**

Generating Comparative Data on Clinical Benefits and Harms of Statins  
to Inform Prescribing Decisions: Evidence from Network Meta-Analyses

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Economics for the degree of Doctor of Philosophy, London, July 2014

## Declaration

I certify that the thesis I have presented for examination for the MPhil/PhD degree of the London School of Economics and Political Science is solely my own work other than where I have clearly indicated that it is the work of others (in which case the extent of any work carried out jointly by me and any other person is clearly identified in it – see ‘Statement of conjoint work’).

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The total word count for this thesis is 78,969 (excluding thesis bibliography and appendix).

## Statement of conjoint work

Part of the work presented in Chapters 4-9 of this thesis has been published<sup>1</sup> or is currently under review<sup>2</sup> in peer-reviewed academic journals, co-authored with Dr. Alec O'Connor from University of Rochester (Rochester NY, USA), Dr. Jasper Brugts from Erasmus Medical Center (Rotterdam, Netherlands), Dr. Rachael Fleurence from the Patient Centered Outcomes Research Institute (Washington DC, USA), Dr. Gert van Valkenhoef from the University of Groningen (Groningen, Netherlands), and Dr. Sofia Dias, Professor Julian Higgins, and Professor Tony Ades from University of Bristol (Bristol, UK) who provided clinical input and guidance on systematic review and statistical analysis methods. For the published aspects of this work, I conceived and designed the studies; identified and selected trials for inclusion in the systematic review; extracted data from included trials; analyzed and interpreted the data; conducted the statistical analyses; interpreted the findings; and drafted the papers. Ms. Bernice Tsoi and Ms. Harleen Toor, who were co-authors on one of the publications, worked in parallel and provided assistance with study identification, selection, and data extraction.

I confirm that I am fully responsible for the entirety of the work presented in this doctoral thesis other than where I have cited the relevant work of others.

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<sup>1</sup> The published papers from this thesis have the following references:

Naci H, Brugts JJ, Fleurence R, Ades T. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. *Eur J Prev Cardiol*. 2013 Aug;20(4):658-70.

Naci H, Brugts JJ, Fleurence R, Tsoi B, Toor H. Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. *Eur J Prev Cardiol*. 2013 Aug;20(4):641-57.

Naci H, Brugts JJ, Fleurence R, Ades T. Comparative effects of statins on major cerebrovascular events: a multiple-treatments meta-analysis of placebo-controlled and active-comparator trials. *QJM*. 2013 Apr;106(4):299-306.

Naci H, Brugts JJ, Ades T. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246,955 participants from 135 randomized, controlled trials. *Circ Cardiovasc Qual Outcomes*. 2013 Jul 1;6(4):390-9.

Naci H, O'Connor AB. Assessing comparative effectiveness of new drugs before approval using prospective network meta-analyses. *J Clin Epidemiol*. 2013 Aug;66(8):812-6.

<sup>2</sup> The following papers are currently under review:

Naci H, Dias S, Ades T. Industry sponsorship bias in research findings: a network meta-analytic exploration of the randomized controlled trials of statins. Under Review.

Naci H, Valkenhoef G, Higgins JPT, Fleurence R, Ades T. Evidence-based prescribing: Using existing data on benefits and harms to choose among multiple drugs. Under Review.

## Other relevant work

During my PhD, I co-authored a number of peer-reviewed publications, which, although highly relevant to the work presented here, did not directly contribute to my thesis. These are listed below:

Fleurence R, Naci H, Jansen JP. The critical role of observational evidence in comparative effectiveness research. *Health Aff (Millwood)*. 2010 Oct;29(10):1826-33.

Sorenson C, Naci H, Cylus J, Mossialos E. Evidence of comparative efficacy should have a formal role in European drug approvals. *BMJ*. 2011 Sep 6;343:d4849.

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Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC Med*. 2013 Jul 4;11:159.

Naci H, Ioannidis JP. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. *BMJ*. 2013 Oct 1;347:f5577.

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Naci H, Ioannidis JP. How Good is "Evidence" from Clinical Studies of Drug Effects and Why Might Such Evidence Fail in the Prediction of Clinical Utility of Drugs? *Annual Review of Pharmacology and Toxicology. In Press*.

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## Abstract

*Background and Importance:* Comparative evidence generated using systematic reviews and meta-analyses can form the basis of high quality prescribing decisions in clinical practice. Such evidence is imperative when choosing a first-line treatment among multiple alternatives, particularly in the United States where there is no single national authority responsible for providing practice guidelines for prescribers.

*Objective:* Using cholesterol-lowering statins as a case study, this thesis set out to evaluate the comparative clinical benefits and harms of statins for the prevention of coronary heart disease.

*Novelty and Empirical Contribution:* The empirical work presented in this thesis was based on a systematic review and network meta-analysis, for the first time combining the placebo-controlled and active-comparator trials of statins. Using 184 randomized trials including 260,630 individuals with or without cardiovascular disease, this thesis makes four major contributions to the literature on the comparative effectiveness and safety of statins, showing the following: (1) cholesterol-lowering effects of statins are less pronounced than suggested by the previous reviews; (2) statins potentially differ in terms of their comparative effects on clinically meaningful benefit outcomes, which are not fully explained by their cholesterol-lowering effects; (3) harms associated with statins are rare; still, some statins are safer than others; and (4) unlike previous findings in the literature, there is no evidence of industry sponsorship bias affecting the trials of statins.

*Implications for Clinical Practice:* Although there are statistically detectable and clinically relevant differences among individual statins, the empirical work presented in this thesis does not conclusively identify a clear winner among statins that should be favored in clinical practice.

*Future Research Directions:* The potential mechanisms underlying the observed differences between individual statins should be investigated in future studies.

*Policy Relevance:* The findings presented in this thesis suggest that statin prescribing patterns over the past decade – and in particular atorvastatin's exceptional sales performance despite its equivalence to simvastatin – are not supported by the current best evidence. A proposed policy option is to raise the bar for market entry of new drugs by requiring comparative evidence at the time of approval decisions. Network meta-analysis methods can be used at the United States Food and Drug Administration setting, thereby making comparative evidence available before prescribing patterns are established.

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- 4S:** Scandinavian Simvastatin Survival Study
- ACAPS:** Asymptomatic Carotid Artery Progression Study
- ACC:** American College of Cardiology
- AFCAPS/TexCAPS:** Air Force/Texas Coronary Atherosclerosis Prevention Study
- AHA:** American Heart Association
- AHRQ:** Agency for Healthcare Research and Quality
- ALERT:** Assessment of Lescol in Renal Transplantation Study
- ALLHAT:** Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
- ALT:** Alanine Transaminase
- ASCOT-LLA:** Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm
- ASPEN:** Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin-Dependent Diabetes Mellitus
- AST:** Aspartate Transaminase
- ATP:** Adult Treatment Panel
- BGR:** Brooks-Gelman-Rubin
- BMJ:** British Medical Journal
- CAIUS:** Carotid Atherosclerosis Italian Ultrasound Study
- CARDS:** Collaborative Atorvastatin Diabetes Study
- CARE:** Cholesterol and Recurrent Events Trial
- CCAIT:** Canadian Coronary Atherosclerosis Intervention Trial
- CELL:** Cost Effectiveness of Lipid Lowering Study
- CER:** Comparative Effectiveness Research
- CI:** Confidence Interval
- CIS:** Multicenter coronary Intervention Study
- CK:** Creatine Kinase
- CLAPT:** Cholesterol Lowering Atherosclerosis PTCA Trial
- CRD:** Centre for Reviews and Dissemination
- CrI:** Credible Interval
- CRISP:** Cholesterol Reduction in Seniors Program
- CURVES:** Comparative Dose Efficacy Study of Atorvastatin versus Statins

**DALI:** Diabetes Atorvastatin Lipid Intervention Study

**DIC:** Deviance Information Criterion

**EMA:** European Medicines Agency

**EXCEL:** Expanded Clinical Evaluation of Lovastatin

**FAST:** Fukuoka Atherosclerosis Trial

**FDA:** Food and Drug Administration

**FLARE:** Fluvastatin Angiographic Restenosis Trial

**GREACE:** Greek Atorvastatin and Coronary-heart-disease Evaluation

**HDL:** High-density Lipoprotein

**HMG-coA:** 3-hydroxy-3-methyl-glutaryl-CoA reductase

**HPS:** Heart Protection Study

**HYRIM:** Hypertension High Risk Management trial

**IDEAL:** Incremental Decrease in Endpoints Through Aggressive Lipid Lowering

**JAMA:** Journal of the American Medical Association

**JUPITER:** Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin

**KAPS:** Kuopio Atherosclerosis Prevention Study

**KLIS:** Kyushu Lipid Intervention Study

**LCAS:** Lipoprotein and Coronary Atherosclerosis Study

**LDL:** Low-density Lipoprotein

**LIPID:** Long-Term Intervention with Pravastatin in Ischaemic Disease Study

**LIPS:** Lescol Intervention Prevention Study

**LRTS:** Lovastatin Restenosis Trial Study

**MAAS:** Multicentre Anti-Atheroma Study

**MARS:** Monitored Atherosclerosis Regression Study

**MEDLINE:** Medical Literature Analysis and Retrieval System Online

**MEGA:** Management of Elevated Cholesterol in Primary Prevention Study

**NICE:** National Institute for Health and Care Excellence

**NCEP:** National Cholesterol Education Program

**PHYLLIS:** Plaque Hypertension Lipid-Lowering Italian Study

**PLAC-I:** Pravastatin Limitation of Atherosclerosis in the Coronary Arteries

**PLAC-II:** Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries

**PMSG:** Pravastatin Multinational Study Group

**Post-CABG:** Post Coronary Artery Bypass Graft Trial

**PREDICT:** Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty

**PREVEND-IT:** Prevention of Renal and Vascular Endstage Disease Intervention Trial

**PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses

**PROSPER:** Pravastatin in Elderly Individuals at Risk of Vascular Disease Trial

**PROSPERO:** International Prospective Register of Systematic Reviews

**REGRESS:** Regression Growth Evaluation Statin Study

**RR:** Relative Risk or Risk Ratio

**SCAT:** Simvastatin/Enalapril Coronary Atherosclerosis Trial

**SPARCL:** Stroke Prevention by Aggressive Reduction in Cholesterol Levels

**STAT:** Simvastatin to Atorvastatin Switch Trial

**STELLAR:** Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin

**STOPP:** Screening Tool of Older Person's Potentially Inappropriate Prescriptions

**TNT:** Treating to New Targets

**WOSCOPS:** West of Scotland Coronary Prevention Study

# Chapter 1

## Introduction:

### The Concept of Quality in Prescription Drug Therapy

Quality in healthcare can be defined as “the extent to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge”.<sup>1</sup> An important aspect of healthcare quality is prescription drug therapy. In the United States alone, about \$230 billion, or 10 percent of the total national healthcare expenditure, was spent on prescription drugs in 2008.<sup>2</sup> Across the European Union countries, spending on prescription drugs accounted for about 19% of total health expenditures in 2010.<sup>3</sup> Prescription drug therapy is not only costly, but also widely common. According to a survey conducted by the United States Centers for Disease Control and Prevention, for example, an estimated half of the adult population in the United States uses at least one prescription drug every month, with one fifth of adult Americans using three or more.<sup>4</sup> The appropriateness of prescribing decisions has major public health and economic implications. Thus, quality of prescription drug therapy is of significant academic and policy interest and forms the focus of this thesis.

#### 1.1 Prescribing Quality

The concept of “prescribing quality” can be viewed from a number of perspectives and its definition varies depending on the perspective of the stakeholder and the target audience. Quality of prescribing can be defined within three different (but not necessarily mutually exclusive) domains. These are patients, governments/payers, and prescribers.

##### 1.1.1 *Patient Perspective*

From a patient’s perspective, quality of prescribing has to do with respecting patient choices and preferences.<sup>5</sup> This domain asks whether a patient’s ‘specifications’ of the goals and parameters of prescribing are considered in prescribing decisions.<sup>6</sup> One aspect of this domain is focused on the prescriber-patient interaction, spanning the range of recommendations by the prescriber that go beyond the specific drug therapy (e.g. lifestyle changes).<sup>7</sup>

Patients increasingly perceive themselves as active consumers of drugs rather than passive recipients. It has been a natural evolution, then, that concomitant with the rise of patients as consumers, patient satisfaction with drug therapy has been promoted as an essential component of quality evaluations. Satisfaction with drug therapy is expected to have an impact on patient adherence to drug therapy.<sup>8-10</sup>

Defining patient perspectives on drug therapy, however, is challenging: choices and preferences are intrinsically different at the individual level, and continue to shift due to external factors. For instance, they may change according to the financial contribution patients have to make to their own healthcare.<sup>11</sup> Similarly, easier access to information influences patient expectations from prescribing.<sup>12-14</sup> Making generalizable inferences on (subjective) patient preferences and their interrelationship with the quality of prescribing is difficult.

#### *1.1.2 Government/Payer Perspective*

From a government/payer's perspective, quality of prescribing is defined in terms of achieving the best attainable health outcomes in relation to the economic costs associated with prescribing. National Health Services Prescription Services in the United Kingdom<sup>15</sup> and Agency for Healthcare Research and Quality in the United States<sup>16</sup> have conducted assessments of prescribing quality from this perspective.

The relevance of defining the quality of prescribing from the government/payer's perspective becomes evident when considering the future cost containment challenges facing healthcare systems across the world. In the United States, for example, prescription drugs constitute one of the fastest growing components of national healthcare spending, as the spending for prescription drugs amounted to \$216.7 billion in 2006 (more than 5 times the \$40.3 billion spent in 1990).<sup>17</sup> It is expected that the government/payer perspective will only become more prominent in the future as the adoption of new (costly) drugs continue to create challenges for health systems. As costs continue to increase, and the healthcare sector continues to come under increased pressure to contain costs, policymakers will question whether the rising level of investment in drugs is an appropriate use of scarce resources.

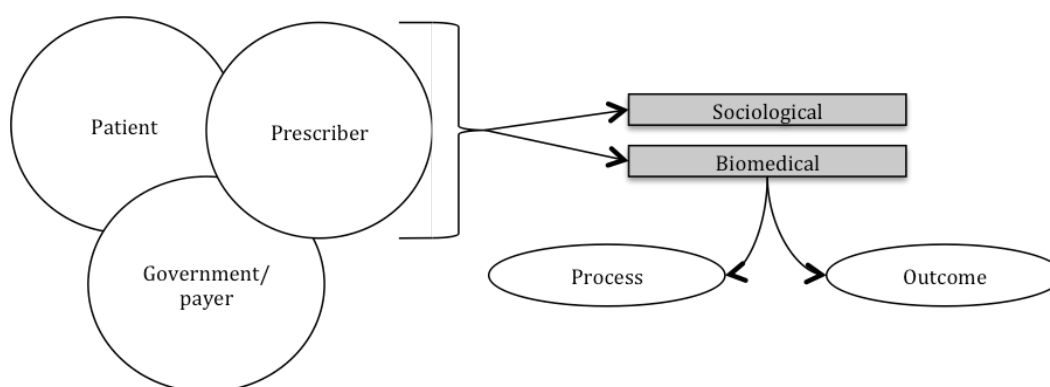
#### *1.2.3 Prescriber Perspective*

Within the complex framework of the prescribing practice, the critical step of the process is the prescriber filling out a prescription form.<sup>18</sup> Quality of prescribing within this domain is defined from two separate but interrelated perspectives: sociological and biomedical. The sociological perspective attempts to shed light on the prescribing behavior of prescribers by gaining a deeper understanding of the interaction between the prescriber's knowledge, attitudes, and beliefs and the subsequent translation of this interaction into prescribing decisions.<sup>19,20</sup>

The biomedical perspective focuses on the biomedical model of disease, which uses an objective (numerical) measurement to define disease, and hence the impact of prescribing on disease.<sup>5</sup> From a biomedical perspective of prescribing, quality can be defined using either process or outcome measures (Figure 1.1). As put forth by Donabedian, “process denotes what is actually done in giving and receiving care.”<sup>21</sup> When applied to prescribing, process measures assess whether the prescription parallels the accepted standards of clinical care within each therapeutic field.<sup>22,23</sup> Outcome denotes the effects of care on the health status of patients and populations.<sup>21</sup>

The context within which patient, government/payer, and prescriber domains interact is unique in the United States, which is the primary country of interest in this thesis (Box 1.1).

**Figure 1.1 – Prescribing Quality Framework.**<sup>3</sup>



### **Box 1.1 Prescription Drug Therapy in the United States**

Several attributes of the fragmented American health care system provide a unique context for the interaction of patient, prescriber, and government/payer perspectives, influencing the nature of prescription drug therapy, and providing an interesting case study for this thesis. For example with the exception of New Zealand, the United States is the only western nation that permits the marketing of pharmaceutical products to consumers in what is commonly termed direct-to-consumer advertising. Responsible for creating and shaping patient demand for prescription drug therapy, such promotional activity is commonly referred to by prescribers as one of the most important factors that affect their decision-making processes and their interactions with patients.<sup>24</sup>

Against a backdrop of escalating costs and few restrictions on the pricing and use of

<sup>3</sup> This framework was developed on the basis of a literature review to define the quality domains associated with prescribing decisions. Discussions with Professor Nick Barber of the School of Pharmacy (University of London) and Professor Tom Walley of Liverpool University were greatly helpful in conceptualizing the interactions between various domains.

pharmaceuticals, the United States – unlike Australia, Canada, and a number of European countries – does not have a single national entity responsible for evaluating prescription drugs for clinical and economic value and making coverage and reimbursement recommendations or decisions. Rather, a number of public and private agencies at the federal, state, and local levels undertake such activities, albeit in an uncoordinated fashion.<sup>25</sup> These include national and local assessments for Medicare, state-level evaluations for Medicaid, and reviews conducted by the Agency for Health Care Research & Quality, Drug Effectiveness Review Project, and clinical specialty organizations. In a similar fashion, there is no national entity tasked with developing authoritative clinical practice guidelines. Of note, such activities were under the purview of The United States Office of Technology Assessment until the 104<sup>th</sup> Congress withdrew funding for it in 1995 due to political and social controversies that still resonate today with the Republican majority in the United States House of Representatives.<sup>25-27</sup> Taken together, this unique context leaves prescribers in the dark about the relative benefits, harms, and costs of seemingly similar drugs, and their appropriate place in therapy.

Recognizing the current lack of authoritative information to guide decisions in clinical practice as a limitation, the United States has recently embarked upon ‘comparative effectiveness research’. The premise of comparative effectiveness research is to improve population health through patient-centered evidence on the comparative effectiveness of interventions, services, and procedures that are used to prevent, diagnose, or treat diseases, disorders, and other health conditions.<sup>28,29</sup> If generated, disseminated, and enforced effectively, this type of evidence has the potential to help patients, prescribers, insurers, pharmacy benefit managers, and policymakers make more informed clinical and health policy decisions.<sup>30</sup>

Given the importance of comparative evidence in effective decision-making, a number of countries explicitly require and use such evidence in making coverage, reimbursement, and prescribing decisions.<sup>31</sup> For example, health technology assessment agencies such as the National Institute for Health and Care Excellence in England and Wales, which is entrusted to make decisions on ‘value for money’ on behalf of the National Health Service, require comparative evidence as inputs to cost-effectiveness analyses, which are in turn used to inform decisions on coverage and reimbursement.<sup>32</sup> However, the use of cost-effectiveness to make coverage recommendations is highly controversial in the United States. In fact, the use of cost-effectiveness is expressly prohibited by the recently enacted health care reform legislation: the founding legislation for the Patient-Centered Outcomes Research Institute states that cost per quality-adjusted life-year thresholds cannot be used as the basis for any coverage and reimbursement determination in

Medicare, the largest public insurance program in the United States.<sup>33,34</sup>

In the United States, comparative effectiveness research is considered worthy of pursuing as long as the focus is purely clinical – “what works” – and not cost-effectiveness. Comparative effectiveness research encompasses efforts that aim to encourage healthcare decision-making (including prescribing decision-making) to be increasingly based on comparative evidence on clinical and humanistic patient-centred outcomes at both the individual and population levels. Therefore, cost considerations do not explicitly enter into the decision-making process for covering, reimbursing, or recommending prescription drugs at least at the national stage. Unlike health technology assessment activities in Australia, Canada, and many European countries, which by definition evaluate both the clinical and economic consequences of prescription drugs (among other health technologies), the focus of comparative effectiveness research in the United States is on clinical evidence.<sup>35</sup>

## 1.2 Prescribing Practice

There are multiple levels of decision-making involved in prescribing practice, which are influenced by the domains of patients, government/payers, and prescribers. Regulatory mechanisms play a pivotal role in prescribing practice, as the multiple levels of decision-making start at the regulatory level. Once a drug receives marketing approval from the Food and Drug Administration in the United States, it is the government/payer domain that operates between manufacturers and consumers and dictates the decision regarding the supply and distribution of drugs. This includes decisions about adding the drug to a specific formulary and the level of reimbursement that may be assigned to it. This level of decision-making is crucial and already influences the number of available drug options the prescriber can choose from for a given condition.

The prescriber is then faced with two decisions: first, *whether* to prescribe at all, and second, *what* to prescribe. Both decisions involve gaining an understanding of the clinical needs of the patient and then applying knowledge and evidence to make a decision.<sup>11</sup> The first decision involves an intricate interplay between the patient and prescriber domains. Within the sociological perspective of prescribing, the decision of whether to prescribe focuses on the patient’s expectations and the prescriber’s perceptions of patient’s expectations.<sup>36,37</sup> The prescriber domain tends to dominate this decision, however, as filling out a prescription form reinforces the authority role of the prescriber, and provides the perception of an unambiguous diagnosis.<sup>11</sup>

If the decision is to prescribe, then the prescriber needs to choose a specific drug to prescribe. This is a difficult task as many drugs are not (at least at first sight) necessarily therapeutically different from each other but are merely extensions of similar drugs. The outcome of this decision has significant implications because the choice of drug has an impact on whether the patient decides to adhere to drug therapy (with health implications). This decision is mainly influenced by the biomedical perspective of prescribing, which emphasizes the tradeoff between the clinical benefit and harm associated with various drug choices. It is, however, ultimately up to the patient to decide whether to have the prescription dispensed, whether to take the drug, and how to take it.<sup>5</sup>

### *1.2.1 Prescribing Quality on the Basis of Indicators*

As highlighted in Figure 1.1, prescribing quality can be defined using process and outcome indicators. Although the ultimate goal of the appropriate use of drugs is to improve clinical outcomes, it is recognized that inferring on the quality of prescribing based on clinical outcome measures has major methodological limitations.<sup>38</sup> This is mainly because many drugs require years of continued adherence before health benefits become measurable. This may be why only a few studies use outcome measures to assess prescribing quality.<sup>39-41</sup> Although a small number of outcome indicators were assessed using administrative claims data in the literature, their validity was not found to be optimal.<sup>42</sup>

As evident by the small number of studies employing outcome measures in the literature, there appears to be a clear preference for using process as opposed to outcome measures. Process measures used in the literature could be classified into two categories: those detecting underprescribing, and those detecting medication errors. Criteria to detect underprescribing usually state that the prescriber failed to prescribe a drug when it was clinically needed.<sup>23</sup> Medication errors include overprescribing (prescribing more drugs than are clinically needed) and misprescribing (incorrectly prescribing drugs that are clinically needed). Criteria to detect overprescribing consist of a list of invalid indications to prescribe a specific drug.<sup>23</sup> Misprescribing criteria include drugs that should be avoided in any circumstances ('drugs-to-avoid' criteria), doses that should not be exceeded, and drugs to avoid in patients with specific disorders.

The most widely used drugs-to-avoid criteria are those that were developed by Beers.<sup>43-45</sup> The criteria include (1) drugs that should be avoided because they are either ineffective or they pose unnecessarily high risk and a safer alternative is available and (2) drugs that should not be used in people with certain comorbidities. In addition to the Beers criteria, the drugs-to-avoid approach also forms the basis of quality indicators of prescribing for the STOPP criteria (Screening Tool of Older Persons' Potentially Inappropriate Prescriptions),<sup>46,47</sup> as well as the Canadian criteria.<sup>48</sup>

### *1.2.2 Prescribing Quality on the Basis of Clinical Practice Guidelines*

Adherence to clinical practice guidelines are used as an alternative approach to guiding prescribing quality.<sup>49</sup> This approach has clear merits, as guidelines constitute an “interface” between evidence and practice and are instrumental in translating research findings into actual practice and reducing variation while improving health outcomes.<sup>50</sup> Guidelines are commonly defined as “systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for clinical circumstances.”<sup>51</sup> During the past two decades, the wide appeal of implementing guidelines as quality assessment tools paralleled the surge of interest in the development and use of these documents. They have been viewed as a “magic bullet” solution to improving clinical practice, which followed the highly publicized efforts to standardize care delivery in the United States.<sup>52</sup> Considerable effort and resources have been spent on the development and dissemination of guidelines<sup>53</sup> and several major medical organizations have put in place processes for developing them.<sup>54-57</sup> A growing body of literature evaluates the quality of prescribing in terms of deviations from guidelines.

Such evaluations show variable results in terms of quality of prescribing.<sup>58-69</sup> In a number of studies, recommendations from guidelines had little effect on prescribing patterns. Lack of adherence to guidelines may be due to extensive criticisms over their recommendations. Unlike their counterparts in many European settings, such as those developed by the National Institute for Health and Care Excellence in England and Wales, recent evaluations in the US demonstrated that guidelines fall considerably short of meeting established methodological standards.<sup>70</sup> It has been shown that recommendations made in United States-based guidelines are largely developed from lower levels of evidence or expert opinion.<sup>71</sup> Additionally, the proportion of recommendations for which there is no conclusive evidence is also growing. Too many of the current guidelines have become marketing and opinion-based pieces, delivering directive rather than assistive statements.<sup>72</sup> Worse, some guidelines offer conflicting recommendations.<sup>73,74</sup>

### *1.2.3 Insights from the Literature*

The literature on prescribing quality highlights the complexity of drug therapy and the challenges facing those evaluating its quality. There are a number of conclusions that can be drawn:

1. *Indicators do not measure prescribing quality: rather, they measure the lack of it.* The literature relying on indicators does not actually assess the quality of prescribing; rather, it assesses the lack of it. Instead of quality of prescribing, an alternative (and more relevant) term to frame the focus of the literature, therefore, would be

‘inappropriateness of prescribing’. This encompasses a range of values and behaviors to express in a simple term the lack of quality of prescribing.<sup>23</sup> Inappropriateness would then refer to medication errors and underprescribing. Within this construct of inappropriateness, most indicators in the literature would be categorized as providing a measurable lower limit of pharmacological inappropriateness (and a floor of quality below which no patient and prescriber should go), rather than a continuous scale of prescribing quality.<sup>23</sup>

2. *Clinical practice guidelines do not provide an ideal platform for guiding prescribing quality.* Even the quality standards based on clinical practice guidelines – those attempting to measure a continuous scale of quality – do not provide an ideal platform for assessing prescribing quality.<sup>75</sup> As guidelines are intended to improve practice by describing a set of actions that should be considered when caring for patients, they are rarely written with retrospective audit of quality in mind. When it comes to guiding prescribing decisions, in particular, most guidelines in the United States leave considerable discretion to prescribers, who are faced with a decision to choose between a large number of (seemingly) equally useful drugs for a given condition. For example, the guidelines developed by the American Academy of Neurology and the Multiple Sclerosis Council failed to distinguish amongst six drugs that are currently used for the treatment of multiple sclerosis, leaving it up to the prescriber to decide how to initiate therapy in multiple sclerosis patients<sup>76</sup> Similar examples spanned across various specialties including mental health (schizophrenia,<sup>77</sup> depression<sup>78</sup>), rheumatology (rheumatoid arthritis<sup>79</sup>), and respiratory illness (asthma<sup>80</sup>). This means that prescribers do not have adequate information about a drug’s appropriate place in practice. Prescribers are expected to sort out the drugs that offer greater benefit with the help of post-marketing observational studies and promotional materials received from the pharmaceutical industry. This ‘flexibility’ of the guidelines in the United States, whether obtained by vagueness or complexity, makes it difficult to choose among multiple drugs to initiate prescription therapy.
3. *Quality standards do not relate to the aspects of prescribing practice that can be fully controlled by prescribers.* Widely used quality standards aimed at assessing the performance of prescribers focus on the aspects of prescribing practice that are not only influenced by prescribers but also by patients. In most assessments, evaluation metrics (based on both indicators and guidelines) focus on the decision of whether to prescribe for a given condition. By quantifying the prescriber’s failure to (correctly) prescribe when drugs are clinically needed, studies mainly target the grey area of prescribing practice where the demands of quality assessments sit uncomfortably with the uncertainties of deciding whether to prescribe. As outlined earlier, deciding *whether* to

prescribe (as opposed to *what* to prescribe) is complex and is informed not only by scientific evidence but also by the patient's expectations and the prescriber's perceptions and knowledge.<sup>81-83</sup> Therefore, making decisions about whether to prescribe requires an optimal tradeoff between clinical benefit and harm within the context of patients' choices and preferences. Since these factors are not fully under the prescriber's control, assessing the prescriber's performance (and judging the quality of prescribing) based on decisions regarding whether to prescribe is not ideal.

### **1.3 Research Opportunity: The Role of Comparative Clinical Evidence in Prescription Drug Therapy**

Quality metrics need to relate to the aspects of prescribing practice that are controlled by prescribers – and measured against an objective benchmark, which is optimally dictated by scientific evidence. One such aspect is choosing a specific drug to prescribe. As there are several possible drugs that are available to treat patients with the same condition, selecting the best drug with which to initiate therapy is a challenging task. One aspect of this is deciding on a specific drug class. Also important is selecting a particular drug within a given class. Albeit the standard thinking that similar drugs do not differ in terms of their clinical efficacy, empirical evidence suggests otherwise.<sup>84</sup> In fact, evidence suggests that assuming that all drugs within a so-called drug class are equivalent and can be used interchangeably may be clinically unwarranted.<sup>85-90</sup>

Given the clinical reality that comparative efficacy of drugs varies, assessing whether prescribers make an effective choice out of the many available similar drugs is important. In order to ensure that the 'right' decision is made in prescribing a specific drug, quality standards need to take into account evidence regarding the comparative effectiveness of similar drugs. As defined by the United States Institute of Medicine, comparative effectiveness evidence "compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care".<sup>28</sup>

Defining prescribing quality on the basis of comparative effectiveness requires prescribers to appraise all the available evidence prior to reaching conclusions about which drug to prescribe. This is unrealistic, as prescribers already cannot keep up with evidence. Previous research has shown that, with the recent explosion in the number of clinical trials and a proliferation of similar drug options, prescribers feel overwhelmed by new evidence; do not know where to look for information; and do not have sufficient time to learn new information.<sup>91,92</sup> Moreover, information on comparative effectiveness is not always available. A randomized controlled trial comparing all similar drugs would provide such information. However, randomized controlled trials are often designed for regulatory purposes and therefore do not include all available comparator drugs. The comparator arms

of randomized controlled trials are often limited to a placebo intervention. In order to obtain insight into the relative efficacy (or safety) of similar drugs, prescribers need to turn to summaries of evidence to discern the most promising drugs from their less effective comparators.

### *1.3.1 The Role of Evidence Review and Synthesis*

Evidence review and synthesis approaches such as systematic reviews and meta-analyses have a clear role in ensuring that healthcare interventions are based on complete and up to date evidence.<sup>93</sup> In terms of prescribing practice, they are essential in assembling evidence on the comparative effectiveness of similar drugs. There is an opportunity to use this evidence to guide the quality of prescribing practice. In theory, this seems straightforward: first a systematic review is conducted to identify all relevant evidence on similar drugs. Then, this evidence is synthesized in a meta-analysis to determine the most efficacious drug and guide prescribing decision-making. This evidence can in turn be used to evaluate whether prescribers are choosing the 'right' drug option when initiating therapy.

In practice, however, there are technical issues to consider that influence the utility of this approach. The first relates to the reliability of the clinical literature. Emerging evidence suggests that the vast majority of published research have weak designs, resulting in biased findings.<sup>94</sup> Equally challenging, the majority of existing tools to synthesize the clinical literature are largely capable of pair-wise, direct comparisons of drugs (often with the comparator being a placebo or control group). This means that comparisons are often limited to two drugs, with simultaneous comparisons of all similar drugs not being feasible. This focus on two drugs makes it difficult for prescribers to determine the best drug among all available comparators. In the absence of meta-analyses that compare all similar drugs of interest, it is not possible to guide and inform prescribing decisions on the basis of pair-wise direct comparisons.<sup>95</sup> The only option is to rely on indirect comparisons.

Methodological advances in statistical synthesis approaches called network meta-analyses (also known as mixed treatment comparisons, multiple-treatments meta-analyses, or multiple treatments comparisons) allow the indirect comparison of multiple treatment options. What distinguishes these methods from pair-wise meta-analyses is that they facilitate the synthesis of a larger pool of evidence by incorporating both direct (when treatments are compared to each other within a trial) and indirect evidence (when treatments are compared between trials with a common comparator treatment, which is often placebo).<sup>96,97</sup> By implication of including both direct and indirect evidence, attempts at statistically synthesizing the existing body of evidence are no longer limited to a comparison of two drugs. Rather, they are capable of comparing all relevant drugs even when they are not trialed against each other.<sup>98</sup> Quantitative comparative effectiveness estimates obtained

from such analyses have the potential to provide prescribers with valuable evidence to make an effective choice out of the many available apparently similar drugs. This thesis focuses on the role of evidence review and synthesis methods to generate comparative evidence, which can subsequently be used to guide high-quality prescribing decisions in clinical practice. As a result, it demonstrates the potential value of evidence review and synthesis approaches in generating comparative effectiveness evidence on individual drugs, and in doing so illustrates how such evidence can fill the existing gaps in clinical practice guidelines.

This work is timely and relevant within the evidence-based medicine framework of the past two decades. Evidence-based medicine is “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.”<sup>99,100</sup> According to Archie Cochrane, current best evidence is “up-to-date information from relevant, valid research about the effects of different forms of health care, the potential for harm from exposure to particular agents”.<sup>101</sup> By synthesizing existing high-quality data on clinical benefits and harms of individual drugs within a therapeutic class, the empirical findings presented in this thesis aim to provide the current best evidence to prescribers who are tasked with choosing among individual drugs.

#### **1.4 Disease Area of Focus: Hypercholesterolemia**

The focus of the empirical work presented in this thesis is on cholesterol-lowering drugs, also known as statins, which are widely prescribed to lower the risk of coronary heart disease and stroke. Currently there are six statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin) marketed for the same indication of “reducing elevated total-cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein-B, non-high-density lipoprotein (non-HDL) cholesterol, and triglyceride levels and increasing high-density lipoprotein (HDL) cholesterol in patients with primary hypercholesterolemia.”<sup>102</sup>

Assessing the comparative effectiveness evidence on statins is crucial for a number of reasons. Statin therapy, initially focused on individuals at high-risk of developing cardiovascular disease, has become widely common as the limits of treatment expanded over time to include persons at progressively lower risk of developing coronary heart disease. While 6.5% of Americans of all ages took cholesterol-lowering medications between 1999 and 2002, the corresponding share of the population was 12.5% between 2007 and 2010, with over 45% of people aged 65 years or older taking cholesterol-lowering medications during this latter period.<sup>103</sup> As the number of individuals in need for statin therapy continues to increase, information regarding the relative clinical value of statins is needed to better inform patients, prescribers, and other healthcare decision makers in clinical practice.

With the basic mechanism of cholesterol lowering remaining the same, the six statins differ to a various extent in pharmacological properties and it would be expected that they differ in terms of their clinical efficacy.<sup>87,104</sup> However, their comparative effectiveness has only been partially documented.<sup>105</sup> Almost all of the meta-analyses conducted on statins assumed that they are equivalent, and hence interchangeable. There has not been any attempt to rank statins on the basis of clinical efficacy (in terms of surrogate outcomes [cholesterol reduction] as well as clinical outcomes [both primary and secondary prevention of coronary heart disease outcomes]), which would greatly assist in evaluating the quality of prescribing decisions.

### **1.5 Thesis Objectives and Overview**

The proponents of the evidence-based medicine movement have called for an increased use of evidence reviews and syntheses to inform prescribing decisions. Existing data from randomized controlled trials is a suitable starting point for guiding drug selection decisions in clinical practice. The overarching objective of this thesis is to synthesize the existing randomized controlled data available in the literature to distinguish among individual statins in terms of clinically meaningful benefit and harm outcomes. As such, it investigates whether synthesizing a disparate body of randomized trial literature would identify a clear winner among multiple treatment options in a given drug class, and provide adequate, valid, and yet simple guidance for decision makers in clinical practice. As discussed in the next chapter (Chapter 2: *Evolution of Clinical Evidence: The Case of Statins*) existing clinical practice guidelines in the United States provide no specific guidance around which statin should be the preferred option to initiate cholesterol-lowering therapy. To address this significant gap, this thesis sets out to examine the comparative clinical benefit and harm profiles of individual statins using existing randomized trial evidence available in the peer-reviewed literature. Specifically, this thesis addressed the following empirical questions:

1. What are the dose-comparative effects of individual statins on cholesterol levels?
2. Are individual statins interchangeable in terms of their effects on clinical benefit outcomes?
3. How do individual statins compare in terms of their side effect profiles?
4. Are the findings of comparative assessments on statins free of industry sponsorship bias?

The methods underpinning the empirical work presented in this thesis are outlined in Chapter 3. Chapters 4-7 address the research questions listed above, and form the main empirical body of the thesis. Chapter 8 brings together key findings with an emphasis on the opportunities and challenges of basing future prescribing decisions on existing clinical evidence. Chapter 9 examines the future research directions and practical policy

recommendations, and proposes regulatory reform for making comparative evidence on clinically meaningful outcomes available at the time of market entry of new drugs. Finally, conclusions are discussed.

## Chapter 2

### Evolution of Clinical Evidence: The Case of Statins

The first HMG-coA reductase inhibitor, lovastatin (originally marketed as Mevacor®), received the Food and Drug Administration's regulatory approval in the United States in July 1987, marking the beginning of the quarter-century history of 'statins' in clinical practice. Dramatically reducing patients' LDL cholesterol levels in clinical trials with an excellent safety and tolerability profile, lovastatin received considerable enthusiasm upon its market entry.

In many aspects, however, this was a newly found enthusiasm – primarily attributed to the emerging consensus to classify total cholesterol, and specifically LDL cholesterol, as an important risk factor for coronary heart disease. Only a little more than a decade before lovastatin received its marketing approval, blood cholesterol levels were not believed to be causally related to coronary heart disease.<sup>106</sup> Termed the “cholesterol controversy”, many were skeptical about the role of cholesterol in the development of coronary heart disease. Clinicians remained opposed to suggestions of any significant relationship between elevated cholesterol levels and coronary heart disease until prospective observational studies such as the Framingham cohort provided an increasingly firm correlation between high serum cholesterol levels and coronary heart disease mortality and morbidity in the early 1980s.<sup>106,107</sup>

So the first statin entered clinical practice during a time when there was emerging interest in cholesterol reduction. Within a decade, this interest turned into widespread – and almost unequivocal – acceptance of lipid-lowering statins as the wonder drugs for coronary heart disease prevention, with statins quickly becoming the most widely prescribed drugs in the United States. In 2005 alone, 173.7 million prescription statin purchases were responsible for \$19.7 billion in expenditures for 29.7 million people.<sup>108</sup> According to latest population-level surveys, roughly one in four Americans aged 45 years or older take a cholesterol-lowering statin drug.<sup>103</sup>

This chapter provides a brief overview of the historical context within which the evidence on statins emerged; how this evidence subsequently shaped the recommendations in influential clinical practice guidelines in the United States; and the role played by meta-analyses in addressing important questions not investigated in individual trials. The case study on statins highlights important questions about the existing approaches to incorporating evidence into clinical practice guidelines; determining the comparative benefits and harms of similar agents; and making clear recommendations as to how decision-makers should make the best use of the existing evidence on different drugs. It also questions the assumption that all drugs in a class are the same for a widely prescribed group of medicines.

## **2.1 Twists and Turns in the Cholesterol Controversy**

Evidence linking elevated cholesterol concentrations (or more accurately, LDL cholesterol) to coronary heart disease emerged first in the form of prospective observational studies,<sup>109</sup> and then in randomized controlled trials.<sup>110</sup> The most influential of the latter was the United States National Institutes of Health Coronary Primary Prevention Trial. This trial demonstrated that lowering LDL cholesterol levels reduced the risk of coronary heart disease morbidity and mortality in men at high risk for coronary heart disease because of raised LDL cholesterol levels.<sup>110</sup>

The United States National Institutes of Health decisively accepted the findings of this trial and, in response, convened a panel of experts to evaluate the new randomized trial evidence within the wider context of the scientific literature. This Consensus Development Conference of the United States National Institutes of Health recommended in 1985 that individuals with high- and moderate-risk blood cholesterol levels should be treated intensively by dietary means, which could be coupled with drug treatment as necessary. Partly reflecting the perceived therapeutic value of existing drug regimens at the time (or the lack thereof), dietary therapy was prioritized over treatment with lipid-lowering drugs. The lipid-lowering armamentarium was limited to bile-acid sequestrants (cholestyramine and colestipol), nicotinic acid (niacin), the fibrates, and probucol. Unfortunately, all of these treatments had limited efficacy or tolerability, or both. Therefore, when lovastatin entered clinical practice, it was hailed as a major advancement over existing lipid-lowering drugs and was widely accepted by patients and clinicians.<sup>111,112</sup> According to its manufacturer's trial reports, lovastatin at its maximum recommended dose of 80 mg/day resulted in estimated mean reductions in LDL cholesterol concentrations of 40%, far greater than any of the treatments available at the time – and with a far more favorable side effect profile.<sup>113,114</sup>

Following the Consensus Development Conference in 1985, the United States National Institutes of Health undertook a massive education and training program and formed the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (which was also termed the Adult Treatment Panel or in short, ATP). Although no specific legislation established this program, it was created under a broad legislative mandate for the National Heart, Lung, and Blood Institute and its predecessor, the National Heart and Lung Institute, to disseminate health information in the form of clinical practice guidelines.<sup>115</sup>

The first report of the NCEP (ATP-I), released in 1988, identified LDL cholesterol as the primary target of clinical management and started to establish the boundaries for therapeutic intervention in high blood cholesterol (also referred to as hypercholesterolemia).<sup>116</sup> It outlined a strategy for the prevention of coronary heart disease in persons with high levels of LDL cholesterol (160 mg/dL) or those with borderline-high LDL cholesterol (130-159 mg/dL) and multiple risk factors such as cigarette smoking and high blood pressure.<sup>117-119</sup> Lipid-lowering drug treatment was recommended after dietary therapy. Although this report recognized the potential added benefit of lovastatin in the treatment of hypercholesterolemia, clinicians were cautioned against its widespread use. This was mainly because the long-term safety of lovastatin was not demonstrated and also it had not been proven to reduce the risk for coronary heart disease when used alone. The report recommended that:

Lovastatin is very effective in lowering LDL cholesterol levels, produces modest reductions in triglyceride levels, and is easy to administer. The clinical use of lovastatin has been under study for only a few years, and its long-term safety and effects on [coronary heart disease] end points have not yet been established. It is, therefore, not classed as a drug of first choice in this report, and some caution is appropriate in its use.

The second report of the NCEP Adult Treatment Panel in 1993 (ATP-II) continued to emphasize LDL cholesterol as the primary target of cholesterol lowering therapy; distinguished between different coronary heart disease risk categories; and emphasized the importance of intensive drug therapy for those individuals with established coronary heart disease (secondary prevention).<sup>120</sup> For individuals without clinically evident coronary heart disease (primary prevention), drug treatment was recommended if LDL cholesterol levels were (1) 190 mg/dL or greater without two other risk factors, or (2) 160 mg/dL or greater with two other risk factors, despite dietary therapy. The goals of drug therapy were the same as those of dietary therapy: to lower LDL cholesterol to below 160 mg/dL or to below 130 mg/dL if two other risk factors were present. For secondary prevention, the goal of therapy was more intensive with LDL cholesterol level of 100 mg/dL or lower. Drug therapy was generally indicated in patients with established coronary heart disease or other

atherosclerotic disease if LDL cholesterol levels were 130 mg/dL or greater after dietary therapy.

Since the first report of the NCEP, simvastatin (originally marketed as Zocor®) and pravastatin (originally marketed as Pravachol®) had received the Food and Drug Administration's marketing approval in 1988 and 1991, respectively. Both of these drugs demonstrated comparable cholesterol-lowering effects to lovastatin and achieved highly effective reductions in LDL cholesterol levels.<sup>121-126</sup> Albeit these promising effects, the second report of the NCEP (ATP-II) continued to caution against the widespread use of these statins given that there was no long-term data available to ascertain their safety.<sup>127</sup> Also, individual randomized trials of statin therapies had not confirmed any survival benefit in terms of total mortality or coronary heart disease mortality. The second report of the NCEP (ATP-II) stated the following:

Statins (lovastatin, pravastatin, and simvastatin) are highly effective in lowering LDL cholesterol. They appear to be relatively safe, but long-term safety remains to be demonstrated. Therefore, they should be used with particular caution in young adult men and premenopausal women. The statins have not been proven to reduce risk for [coronary heart disease] when used alone, but in view of their efficacy for lowering LDL cholesterol, they are attractive for treatment of severe forms of hypercholesterolemia and for maximal lowering of LDL levels in secondary prevention.

## **2.2 The Lipid Hypothesis: Controversy No More**

By the early 1990s, the first component of the lipid hypothesis – that elevated cholesterol levels are causally linked with a high risk of atherosclerosis and subsequent coronary heart disease – was well accepted. However, its second component, which asserts that lowering cholesterol levels can lower the risk of coronary heart disease, and as a result total mortality, remained controversial. Earlier reviews on this topic cautioned against drug treatment in patients with low to moderate risk of death from coronary heart disease because of possible increases in all-cause mortality with treatment.<sup>128</sup> As evidence on the benefits of lipid lowering therapy (including drug classes other than statins) continued to emerge, there remained important unanswered questions. Importantly, no previous trial of lipid-lowering therapy had demonstrated a reduction of risk for total mortality. Also, there were concerns about possible increases in some non-cardiovascular causes of mortality associated with cholesterol lowering.<sup>129,130</sup> A review published in 1990 showed a significantly increased risk of death from accidents and violence when the results of six randomized trials of lipid lowering drugs (including non-statin drug classes) were pooled.<sup>129</sup> This finding spurred considerable debate and led a number of influential cardiologists to ask: "Should there be a moratorium on the use of cholesterol lowering drugs?"<sup>130</sup>

The publication in 1994 of the results of the Scandinavian Simvastatin Survival Study (4S) marked a turning point in the cholesterol controversy.<sup>131</sup> In this study of 4,444 individuals with established coronary heart disease (secondary prevention), simvastatin produced highly significant reductions in the risk of death and morbidity after five years of follow-up. There was a 30% reduction in all-cause mortality (due to a 42% reduction in coronary deaths), 34% reduction in major coronary events and a 37% reduction in revascularization procedures. Importantly, there was no indication of any increase in non-cardiovascular mortality. These results reassured those who had remained skeptical to cholesterol-lowering therapy and led Michael Oliver, a prominent Professor of Cardiology in the United Kingdom, to recommend in the British Medical Journal: “Lower patients’ cholesterol now.”<sup>132</sup>

Later large randomized controlled trials of atorvastatin<sup>133</sup> (which gained market approval in 1997 as Lipitor®), fluvastatin<sup>134</sup> (which gained market approval in 1994 as Lescol®), lovastatin,<sup>135</sup> pravastatin,<sup>136-138</sup> and simvastatin<sup>139</sup> further distinguished statins from other lipid lowering drugs and established that statins not only substantially reduced the risk of cardiovascular events, but did so without any increase in non-cardiovascular mortality. According to these large trials, statins reduced the risk of coronary heart disease events both in patients with established coronary heart disease (secondary prevention)<sup>131,133,134,139</sup> and in those without (primary prevention).<sup>135,136,139</sup>

Taken together, large statin trials contributed to the understanding that the cholesterol controversy was conclusively over.<sup>140</sup> Today, it is widely accepted that elevated serum cholesterol levels are an established risk factor for cardiovascular disease: LDL cholesterol lowering decreases the risk of coronary heart disease mortality and morbidity.<sup>141-147</sup> A strong body of clinical trial, epidemiological, and genetic literature has shown that lifetime risk of coronary heart disease increases sharply with higher LDL cholesterol levels for men and women at all ages.<sup>144,148-151</sup> The relation between LDL cholesterol and coronary heart disease risk appears to be continuous.<sup>152</sup> In addition, net decreases in LDL cholesterol translate log-linearly to net decreases in coronary heart disease and total mortality risk.<sup>153</sup>

In light of this accumulating evidence, the clinical practice guidelines today unequivocally recommend the use of statins in clinical practice for some patients with coronary heart disease or equivalent. According to the third NCEP Adult Treatment Panel guidelines (ATP-III),<sup>154</sup> persons with coronary heart disease or coronary heart disease risk equivalent<sup>4</sup> (collectively referred to as *high-risk*) have an LDL cholesterol goal of <100 mg/dL. In this

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<sup>4</sup> The notion of risk equivalence suggests that individuals with certain characteristics share the same risk for coronary heart disease. For instance, persons with diabetes without coronary heart disease (most of whom display multiple risk factors) are considered to have the risk level of coronary heart disease risk equivalent.

group of individuals with LDL cholesterol  $\geq 100$  mg/dL dietary therapy is recommended. When baseline LDL cholesterol is  $\geq 130$  mg/dL, an LDL-lowering drug is recommended in addition to dietary therapy. Those with multiple risk factors (considered *moderately high-risk*) have an LDL cholesterol goal of  $<130$  mg/dL. Finally, those with 0–1 risk factor have a goal LDL cholesterol of  $<160$  mg/dL, for which clinical management and dietary therapy are recommended if LDL cholesterol levels are  $\geq 160$  mg/dL.

As it applies to lipid lowering drug therapy, the third report of the NCEP was particularly important in two ways. First, it emphasized the importance of (more) intensive LDL cholesterol lowering targets. Second, it highlighted the role of lipid-lowering drugs, and particularly statins, in achieving these intensive targets. Although the report acknowledged the potential relevance of non-statin drugs such as bile acid sequestrants and nicotinic acid, statins at moderate doses are considered as first-line drug therapy. The report stated the following:

HMG-coA reductase inhibitors (statins) are powerful LDL-lowering drugs. Statin therapy reduces risk for [coronary heart disease] outcomes in both primary and secondary prevention... Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.

Lipid-lowering recommendations of the ATP-III national guidelines had an impact on clinical practice and prescription rates for statins in the United States surged immediately after the publication of the ATP-III report in 2001. An estimated 12.5 million Americans (19.6% of the adult population with high LDL cholesterol levels) were prescribed statins during the period right before the publication of the clinical practice guidelines. However, the number of individuals receiving statins increased to 24 million between 2003 and 2004, which was an estimated 35.9% of United States adults with high LDL cholesterol levels.<sup>155</sup> Partly as a result of the NCEP ATP guidelines, statins are currently the mainstay of therapeutic management of high blood cholesterol levels for the prevention of coronary heart disease.

In November 2013 (following the completion of the full draft of this thesis), the American College of Cardiology and American Heart Association (ACC/AHA) issued a new clinical practice guideline on the treatment of blood cholesterol to reduce cardiovascular disease risk.<sup>156-158</sup> These guidelines abandoned specific LDL levels as treatment goals;<sup>159,160</sup> lowered the threshold of statin treatment and recommended drug therapy for the primary prevention of coronary heart disease;<sup>161,162</sup> and recommended the use of a newly developed pooled cohort equations for estimating 10-year coronary heart disease risk.<sup>163,164</sup> By doing so, the latest clinical practice guidelines generated substantial controversy, leaving patients and prescribers perplexed – particularly when the new risk estimator was subsequently found to be erroneous,<sup>165,166</sup> further fuelling fierce debate and intense criticism.<sup>167-170</sup>

According to the ACC/AHA report, 33 million Americans are expected to be newly eligible for high-intensity statin therapy while statins will be considered for another 13 million Americans under the new guidelines.<sup>157,162</sup> Such considerable broadening of pharmacological therapy underscores the importance of evaluating the comparative benefits and harms associated with individual statins.

## **2.3 Piecing Together the Evidence on Statins: Meta-Analyses of Randomized Trials**

Although the quickly expanding literature on statins overwhelmingly confirmed the overall benefits of statins in the general population, evidence on their effect in certain patient sub-populations was less certain in some trials. For instance, until recently, the effect of statins on the elderly was a matter of continuing debate. In addition, there was continuing interest in investigating the impact of statins on major cerebrovascular events such as strokes, which had not been evaluated in individual trials. A matter of considerable debate, it was not clear whether statins resulted in a survival benefit in individuals without established coronary heart disease (for primary prevention). To address these questions, a large number of meta-analyses pieced together the findings of numerous trials and provided further insights into the effectiveness of statins on various outcomes across a range of patient populations. Although the findings of different meta-analyses are not directly comparable (due to variability in trial inclusion criteria and clinical outcomes considered), the remaining part of this chapter provides a review of these meta-analyses and demonstrates how these analyses played a key role in not only synthesizing the evidence base but also in answering important questions not fully addressed in individual trials.

### *2.3.1 Quantifying the Overall Benefits of Statins*

Without differentiating between primary and secondary prevention populations, earlier meta-analyses of statin trials showed that individuals receiving statins experienced significant reductions in the risk of total mortality and major coronary events (Table 2.1). As early as 1997, the analysis by Hebert and colleagues examined whether cholesterol lowering with statins reduced the risk for total mortality, as was the case in large trials. On the basis of 16 trials including approximately 20,000 individuals with predominantly established coronary heart disease treated and followed up for an average of 3.3 years, there were significant reductions in risks of total mortality of 22% (95% CI: 12% to 31%).<sup>171</sup> In 1999, the meta-analysis by LaRosa and colleagues estimated the risk reduction of major coronary events and total mortality associated with statin drug treatment in five trials with 30,817 individuals. Findings of this meta-analysis confirmed that reductions in LDL cholesterol associated with statin drug treatment resulted in roughly 30% decline in coronary events and 16% decline in total mortality.<sup>172</sup> Similarly, in another meta-analysis published in 1999, Ross and colleagues reviewed 17 trials with 21,303 individuals and reported that patients

who received statin treatment demonstrated a 20% to 30% reduction in all-cause mortality and major cardiovascular events compared with patients who received placebo.<sup>173</sup> In 2003, the meta-analysis by Cheung and colleagues included 79,494 individuals and showed that statins led to reductions in major coronary events by 27% (95% CI: 23% to 30%) and all-cause mortality by 15% (95% CI: 8% to 21%).<sup>174</sup> In 2005, one of the most comprehensive reviews to date, the Cholesterol Treatment Trialists conducted a prospectively planned, individual patient-level meta-analysis on 90,056 individuals enrolled in 14 randomized trials.<sup>175</sup> In this analysis, there was a 12% reduction in the relative risk for all-cause mortality (95% CI: 9% to 16%), 19% reduction in coronary mortality (95% CI: 15% to 21%), and 23% reduction in major coronary events (95% CI: 20% to 26%).

Focusing specifically on secondary prevention trials, the analysis by Wilt and colleagues (2004) showed that statin therapy lowered the risk of all-cause mortality (RR: 0.84, 95% CI: 0.79 to 0.89), major coronary events (RR: 0.75, 95% CI: 0.71 to 0.79), and coronary heart disease mortality (RR: 0.77, 95% CI: 0.71 to 0.83) on the basis of 25 trials enrolling 69,511 individuals with established coronary heart disease.<sup>176</sup>

Although observational studies had not identified hypercholesterolemia as a major risk factor for stroke,<sup>72</sup> meta-analyses of randomized trials that evaluated the effects of statins on stroke prevention in patients with and without coronary heart disease found that statins were effective in reducing fatal and nonfatal strokes.<sup>177-179</sup> These reviews suggested a role for statins in stroke prevention independent of coronary heart disease risk reduction or cholesterol levels.<sup>148</sup>

**Table 2.1** – Effect of statins compared to control on all-cause mortality in published meta-analyses of individuals with and without coronary heart disease.

Source (Year Published)	Hebert et al. (1997) <sup>171</sup>	LaRosa et al. (1999) <sup>172</sup>	Ross et al. (1999) <sup>173</sup>	Cheung et al. (2004) <sup>174</sup>	Wilt et al. (2004) <sup>176</sup>
Inclusion criteria	Reporting total mortality and strokes	Follow-up ≥ 4 years	Follow-up ≥ 1 year	Follow-up ≥ 3 years ≥ 100 major coronary events	Secondary prevention ≥ 100 individuals per trial arm
# of trials/ individuals	16 trials n = 29,008	5 trials n = 30,817	17 trials n = 21,303	10 trials n = 79,494	25 trials n = 69,511
Effect on all-cause mortality (95% CI)	OR 0.78 (0.69, 0.88)	OR 0.79 (0.72, 0.86)	OR 0.76 (0.67, 0.86)	RR 0.85 (0.79, 0.92)	RR 0.84 (0.79, 0.89)
Effect on major coronary events (95% CI)	OR 0.67 (0.61, 0.73)	OR 0.64 (0.57, 0.79)	Not available	RR 0.73 (0.70, 0.77)	RR 0.75 (0.71, 0.79)
Effect on major strokes (95% CI)	OR 0.71 (0.59, 0.86)	Not available	Not available	RR 0.82 (0.75, 0.90)	Not available
Trials included	4S; WOSCOPS; CARE; Sahni et al. <sup>180</sup> ; EXCEL; MARS; Jones et al. <sup>181</sup> ; PMSG; CCAIT; PLAC-I; PLAC-II; MAAS; ACAPS; LRTS; REGRESS; KAPS	4S; WOSCOPS; CARE; AFCAPS; TexCAPS; LIPID	4S; WOSCOPS; CARE; CAIUS; CRISP; Chan et al. <sup>182</sup> ; PMSG; CCAIT; REGRESS; CIS; ACAPS; KAPS; PLAC-I; PLAC-II; MAAS	4S; WOSCOPS; CARE; AFCAPS/ TexCAPS; LIPID; HPS; LIPS; PROSPER; ASCOT-LLA; ALLHAT-LLA	4S; CARE; LIPID; PLAC-I; PLAC-II; PMSG; PROSPER; REGRESS; PREDICT; CIS; HPS; MAAS; SCAT; CCAIT; MARS; LRTS; LCAS; LIPS; Riegger et al. <sup>183</sup> ; FLARE; CLAPT; ALLHAT-LLA; GREACE; Post-CABG; TARGET TANGIBLE <sup>184</sup>

**4S:** Scandinavian Simvastatin Survival Study<sup>131</sup>; **ACAPS:** Asymptomatic Carotid Artery Progression Study<sup>185</sup>; **AFCAPS/TexCAPS:** Air Force/Texas Coronary Atherosclerosis Prevention Study<sup>135</sup>; **ALLHAT-LLA:** Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid Lowering Arm<sup>186</sup>; **ASCOT-LLA:** Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm<sup>133</sup>; **CAIUS:** Carotid Atherosclerosis Italian Ultrasound Study<sup>187</sup>; **CARE:** Cholesterol and Recurrent Events Trial<sup>137</sup>; **CCAIT:** Canadian Coronary Atherosclerosis Intervention Trial<sup>188</sup>; **CIS:** Multicenter coronary Intervention Study<sup>189</sup>; **CLAPT:** Cholesterol Lowering Atherosclerosis PTCA Trial<sup>190</sup>; **CRISP:** Cholesterol Reduction in Seniors Program<sup>191</sup>; **EXCEL:** Expanded Clinical Evaluation of Lovastatin<sup>192</sup>; **FLARE:** Fluvastatin Angiographic Restenosis Trial<sup>193</sup>; **GREACE:** Greek Atorvastatin and Coronary-heart-disease Evaluation<sup>194</sup>; **HPS:** Heart Protection Study<sup>139</sup>; **KAPS:** Kuopio Atherosclerosis Prevention Study<sup>195</sup>; **LCAS:** Lipoprotein and Coronary Atherosclerosis Study<sup>196</sup>; **LIPID:** Long-Term Intervention with Pravastatin in Ischaemic Disease Study<sup>138</sup>; **LIPS:** Lescol Intervention Prevention Study<sup>134</sup>; **LRTS:** Lovastatin Restenosis Trial Study<sup>197</sup>; **MAAS:** Multicentre Anti-Atheroma Study<sup>198</sup>; **MARS:** Monitored Atherosclerosis Regression Study<sup>199</sup>; **PLAC-I:** Pravastatin Limitation of Atherosclerosis in the Coronary Arteries<sup>200</sup>; **PLAC-II:** Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries<sup>201</sup>; **PMSG:** Pravastatin Multinational Study Group<sup>125</sup>; **Post-CABG:** Post Coronary Artery Bypass Graft Trial<sup>202</sup>; **PREDICT:** Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty<sup>203</sup>; **PROSPER:** Pravastatin in Elderly Individuals at Risk of Vascular Disease Trial<sup>204</sup>; **REGRESS:** Regression Growth Evaluation Statin Study<sup>205</sup>; **SCAT:** Simvastatin/Enalapril Coronary Atherosclerosis Trial<sup>206</sup>; **WOSCOPS:** West of Scotland Coronary Prevention Study<sup>136</sup>

### 2.3.2 *Statin Therapy for the Elderly*

As the overall benefits of statins in the prevention of coronary heart disease mortality and morbidity became increasingly clear for middle-aged individuals, an important question remained about the therapeutic value of statin therapy in the elderly. According to observational studies, there appeared to be a lack of association between cholesterol and coronary heart disease mortality and morbidity in persons older than 70 years.<sup>207</sup> Also, PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease Trial), which was the first large trial of statins that specifically enrolled older participants, did not demonstrate a reduction in all-cause mortality risk,<sup>204</sup> potentially resulting in suboptimal utilization of statins among the elderly.<sup>208,209</sup> Roberts and colleagues performed one of the first reviews of statin trials in the elderly and showed that statin therapy is effective in reducing all-cause mortality and cardiovascular outcomes, including myocardial infarctions, coronary heart disease death, and stroke in this population. The findings of this meta-analysis were confirmed in a later review by Afalo and colleagues, which showed that statins reduce all-cause mortality by 22% and coronary heart disease mortality by 30% in elderly patients with documented coronary heart disease. More recent reviews also supported the use of statins in the elderly.<sup>210</sup>

### 2.3.3 *Statins for the Primary Prevention of Coronary Heart Disease*

In contrast to the clear and consistent findings of the meta-analyses that did not differentiate between primary and secondary prevention populations, meta-analyses that specifically focused on primary prevention trials yielded less certain results and led to considerable debate that continues to date.<sup>161,211</sup> According to these meta-analyses, statins reduced the risk of major coronary events and major cerebrovascular events but their effect on all-cause mortality appeared non-significant in some meta-analyses and marginally significant in others (Table 2.2).

Pignone and colleagues performed one of the earliest meta-analyses of statin drug treatment for individuals without established coronary heart disease in 2000.<sup>212</sup> This study showed that there was an 11% statistically non-significant reduction in the risk for all-cause mortality in three statins trials with 14,119 individuals (95% CI: 25% reduction to 6% increase) while there was a significant reduction in the risk for major coronary events (OR: 0.65, 95% CI: 0.55, 0.77).

Although there was no trial evidence to suggest that primary prevention would have overall survival benefits (i.e. an effect on extending life), the NCEP ATP-III strongly recommended the use of lipid-lowering drugs in this population. This was with the understanding that the

benefits of proactively reducing the risk for coronary heart disease would outweigh the risks – particularly because the prevention of coronary events would also prevent individuals from graduating into a considerably higher risk category. The third report of the NCEP ATP stated that:

LDL lowering therapy should play an important role in primary prevention of [coronary heart disease] in persons at increased risk... [D]rugs should be considered when LDL levels are high ( $\geq 160$  mg/dL). For higher risk persons with multiple risk factors..., consideration should be given to drug therapy when the LDL goal ( $<130$  mg/dL) cannot be achieved by lifestyle therapies. Finally, multiple-risk-factor persons at highest risk (10-year risk  $>20$  percent) need to attain even lower LDL cholesterol levels (LDL goal  $<100$  mg/dL), and consideration should be given to starting drug therapy simultaneously with therapeutic lifestyle.

Following the publication of the NCEP clinical practice guidelines, the results of large primary prevention trials became available. The publication of the findings of these trials added to the confusion around the benefits of statins because there emerged an apparent inconsistency around the benefit of statins among individuals with no symptomatic coronary heart disease. Although statins significantly reduced the risk of major coronary events in the earlier trials such as AFCAPS/TexCAPS (Air Force - Texas Coronary Atherosclerosis Prevention Study)<sup>135</sup> and WOSCOPS (West of Scotland Coronary Prevention Study),<sup>136</sup> they had no impact on this outcome in later trials: PROSPER<sup>204</sup> and ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial).<sup>186</sup> Similarly, their effect on total mortality was still not certain in large trials.

To clarify the role of statins for the primary prevention of coronary heart disease, additional meta-analyses were performed. The review by Thavendiranathan and colleagues included 42,848 individuals from seven trials and showed that statin therapy decreased the incidence of major coronary events but not coronary heart disease or overall mortality (RR: 0.93, 95% CI: 0.86 to 1.01).<sup>213</sup> In their meta-analysis, Mills and colleagues found a significant 7% reduction in the relative risk of all-cause mortality (95% CI: 1% to 13%) based on 20 trials with predominantly primary prevention populations.<sup>214</sup> This meta-analysis also showed a significant 11% reduction in cardiovascular deaths (95% CI: 2% to 19%). Ward and colleagues obtained a similarly significant survival benefit in their meta-analysis conducted for the United Kingdom National Health Service Research & Development Health Technology Assessment Program.<sup>215</sup>

The publication in 2008 of the findings of the large-scale JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial provided evidence in support of statins in primary prevention. In JUPITER, 17,802 healthy men and women with normal LDL cholesterol levels were randomized to receive

rosuvastatin (which gained marketing approval in 2003 as Crestor®) and placebo.<sup>216</sup> There was a 20% reduction in the risk for all-cause mortality in individuals randomized to rosuvastatin as compared to placebo (95% CI: 3% to 33%) with substantial reductions in the composite endpoint of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. However, this trial was stopped early once the survival benefits of rosuvastatin emerged, which may have exaggerated its findings.<sup>217,218</sup> Indeed, the trial investigators acknowledged that the effect size observed in this trial was more pronounced than what was expected according to previous meta-analyses. Prominent researchers subsequently questioned the validity of the findings of this trial.<sup>219</sup>

Taking into account the findings of the JUPITER trial, Brugts and colleagues performed a meta-analysis of the primary prevention trials and estimated that the survival benefit of statin therapy was a significant 12% reduction in the odds of all-cause mortality (95% CI: 4% to 19%) on the basis of 70,388 individuals enrolled in 10 trials after a follow-up period of 4.1 years.<sup>220</sup> The analysis conducted by Ray and colleagues (2010) conflicted the findings of the Brugts analysis and suggested that there did not appear to be a statistically significant survival benefit of receiving statins in primary prevention.<sup>221</sup> In this analysis, the relative risk of all-cause mortality when comparing statins versus placebo was 0.91 (95% CI: 0.81 to 1.01) based on 10 trials with 65,229 high-risk individuals with no established disease after 3.7 years of follow-up. Unfortunately, an analysis of cardiovascular morbidity was not undertaken. Further complicating the issue, the review conducted by the Cochrane Collaboration (2011) showed that statins reduced the risk of all-cause mortality (relative risk: 0.83, 95% CI: 0.73 to 0.95) as well as the combined fatal and non-fatal cardiovascular endpoints (relative risk: 0.70, 95% CI: 0.61, 0.79).<sup>222</sup>

The apparent inconsistency in the results across the most recent meta-analyses of primary prevention trials could be attributed to differences in the study selection criteria adopted in different analyses. For instance, the analysis by Mills and colleagues included trials which had a greater than 50% primary prevention population.<sup>214</sup> By the standards of more recent meta-analyses, the meta-analysis by Mills et al. included a large number of individuals with established coronary heart disease, which likely overestimated the true benefits in the primary prevention setting. The meta-analysis performed by Brugts and colleagues included trials if they enrolled at least 80% or more participants without established cardiovascular disease.<sup>220</sup> Ray and colleagues sought unpublished information from the investigators of the corresponding clinical trials to ensure that the analysis included a strictly primary prevention population.<sup>221</sup> The Cochrane Collaboration's review included trials if 90% or more of participants had a history of coronary heart disease.<sup>222</sup>

**Table 2.2** – Effect of statins compared to control on all-cause mortality in published meta-analyses of individuals without coronary heart disease (primary prevention population).

Source (Year Published)	Pignone et al. (2000) <sup>212</sup>	Thavendiran athan et al. (2006) <sup>213</sup>	Mills et al. (2008) <sup>214</sup>	Ward et al. (2007) <sup>215</sup>	Brugts et al. (2009) <sup>220</sup>	Taylor et al. (2011) <sup>222</sup>
<b>Inclusion criteria</b>	Follow up ≥ 1 year  Patients with no known coronary heart disease	Follow up ≥ 1 year  80% or more without cardiovascular disease	Follow up ≥ 1 year  50% or more without coronary heart disease	Patients with no known coronary heart disease	Follow up ≥ 1 year  80% or more without coronary heart disease	Follow up ≥ 6 months  90% or more without coronary heart disease
<b># of trials/ individuals</b>	3 trials n = 14,119	7 trials n = 42,848	20 trials n = 66,001	4 trials n = 13,665	10 trials n = 70,388	14 trials n = 34,272
<b>Effect on all-cause mortality (95% CI)</b>	OR 0.89 (0.75, 1.06)	RR 0.92 (0.84, 1.01)	RR 0.93 (0.87, 0.99)	RR 0.83 (0.70, 0.98)	OR 0.88 (0.81, 0.96)	RR 0.83 (0.73-0.95)
<b>Effect on major coronary events (95% CI)</b>	OR 0.65 (0.55, 0.77)	RR 0.71 (0.60, 0.83)	Not estimated	RR 0.64 (0.50, 0.82)	OR 0.70 (0.61, 0.81)	RR 0.72 (0.65-0.79)
<b>Effect on strokes (95% CI)</b>	Not available	RR 0.86 (0.75, 0.97)	RR 0.88 (0.78, 1.00)	Not estimated.	OR 0.81 (0.71, 0.93)	RR 0.78 (0.65-0.94)
<b>Trials included</b>	ACAPS; WOSCOPS; AFCAPS/ TexCAPS	WOSCOPS; AFCAPS/ TexCAPS; PROSPER; ALLHAT- LLA; ASCOT- LLA; HPS; CARDS	ACAPS; ALERT; AFCAPS/ TexCAPS; ALLHAT-LLT; ASCOT-LLA; ASPEN; CAIUS; CARDS; FAST; HYRIM; KAPS; MEGA; PREVEND-IT; PROSPER; WOSCOPS; PHYLLIS; Mohler et al. <sup>223</sup> ; PMSG; KLIS	CAIUS; CARDS; ASCOT-LLA; DALI <sup>224</sup>	WOSCOPS; AFCAPS/ TexCAPS; PROSPER; ALLHAT- LLA; ASCOT- LLA; HPS; CARDS; ASPEN; MEGA; JUPITER	ACAPS; AFCAPS/ TexCAPS; ASPEN; CAIUS; CARDS; CELL; Derosa et al. <sup>225</sup> ; HPS ; KAPS; MEGA; PHYLLIS A; PHYLLIS B; PREVEND-IT; WOSCOPS

**ACAPS:** Asymptomatic Carotid Artery Progression Study<sup>185</sup>; **AFCAPS/TexCAPS:** Air Force/Texas Coronary Atherosclerosis Prevention Study<sup>135</sup>; **ALERT:** Assessment of Lescol in Renal Transplantation Study<sup>226</sup>; **ALLHAT:** Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid Lowering Arm<sup>186</sup>; **ASCOT:** Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm<sup>133</sup>; **ASPEN:** Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus<sup>227</sup>; **CAIUS:** Carotid Atherosclerosis Italian Ultrasound Study<sup>187</sup>; **CARDS:** Collaborative Atorvastatin Diabetes Study<sup>228</sup>; **CELL:** Cost Effectiveness of Lipid Lowering Study<sup>229</sup>; **DALI:** Diabetes Atorvastatin Lipid Intervention Study<sup>224</sup>; **FAST:** Fukuoka Atherosclerosis Trial<sup>230</sup>; **HPS:** Heart Protection Study<sup>139</sup>; **HYRIM:** Hypertension High Risk Management trial<sup>231</sup>; **JUPITER:** Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin<sup>232</sup>; **KAPS:** Kuopio Atherosclerosis Prevention Study<sup>195</sup>; **KLIS:** Kyushu Lipid Intervention Study<sup>233</sup>; **MEGA:** Management of Elevated Cholesterol in Primary Prevention Study Group<sup>125</sup>; **PREVEND-IT:** Prevention of Renal and Vascular Endstage Disease Intervention Trial<sup>236</sup>; **PROSPER:** Pravastatin in Elderly Individuals at Risk of Vascular Disease Trial<sup>204</sup>; **WOSCOPS:** West of Scotland Coronary Prevention Study<sup>136</sup>

Given this inconsistency in the evidence, the benefit of prescribing statin therapy in individuals without established coronary heart disease has continued to spur considerable debate. At the center of this debate was the question of whether the risk cut-off between primary and secondary prevention populations was justified. This question is still relevant today as most candidates for primary prevention have a certain level of cardiovascular risk, although by definition they have not had a cardiovascular event yet. It is increasingly understood that those who are considered for treatment as primary prevention may already be at an advanced stage of atherosclerosis (i.e. hardening of the arteries). This suggests that patients may need to be considered to be on a continuum of atherosclerosis, instead of clear-cut categories of primary and secondary prevention. In the words of Minder et al.: “we question why the addition of a statin the day after a myocardial infarction [which is considered secondary prevention] is considered more effective than its addition in the preceding week, month, or year [which is considered as primary prevention].”<sup>237</sup>

The individual patient-level meta-analysis, performed by the Cholesterol Treatment Trialists’ Collaboration and published in 2012, arguably ended this controversy by demonstrating the benefit of statins in individuals with no established coronary heart disease. Based on data on 174,149 individuals from 27 trials, their rigorous analysis showed that statins resulted in reductions in the risk for major coronary events (relative risk: 0.76, 95% CI: 0.73 to 0.79) and all-cause mortality (relative risk: 0.91, 95% CI: 0.85 to 0.97).<sup>238</sup> This analysis provided strong evidence that statin therapy was effective even in individuals at very low risk categories. This meta-analysis contributed to the recommendation in the latest ACC/AHA guidelines that individuals without established coronary heart disease should be considered for statin therapy.<sup>164</sup>

#### *2.3.4 LDL Cholesterol Levels: Is Lower Better?*

Although statins differ in terms of their multiple effects on the cardiovascular system (termed pleiotropic effects), there is widespread acceptance that they exert their beneficial effects primarily by reducing the level of LDL cholesterol.<sup>239</sup> Also, the reductions in the risk of cardiovascular events achieved by statin therapy appear to be similar regardless of baseline cholesterol levels. There does not appear to be a LDL cholesterol threshold below which no further reduction in risk occurs.

A number of randomized controlled trials reported greater risk reductions with more intensive statin regimens resulting in greater reductions in LDL cholesterol, as compared to more moderate regimens. In light of these findings, a 2004 update of the NCEP ATP-III guidelines recommended more intensive lipid lowering for high-risk individuals: LDL cholesterol goal of <70 mg/dL became a therapeutic option, i.e., a reasonable clinical

strategy, for individuals at high risk of developing coronary heart disease – even for individuals who have a baseline LDL cholesterol <100 mg/dL. The treatment threshold for moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%) was similarly lowered and an LDL cholesterol goal <100 mg/dL was recommended as a therapeutic option.

Later meta-analyses corroborated the notion that lower LDL cholesterol levels would result in greater risk reductions. For example, Cannon and colleagues compared the reduction of cardiovascular outcomes with high-dose statin therapy vs. standard dosing and found that there was a significant 16% odds reduction in major coronary events among 27,548 individuals in four large trials.<sup>240</sup> Similarly, Josan and colleagues performed a systematic review and meta-analysis to examine the evidence for the benefits of intensive statin therapy in patients with coronary heart disease.<sup>241</sup> On the basis of seven trials including 29,395 individuals, more intensive regimens reduced the odds of myocardial infarctions (OR: 0.83, 95% CI: 0.77 to 0.91) and stroke (OR: 0.82, 95% CI: 0.71 to 0.95), but not total mortality (OR: 0.96, 95% CI: 0.80 to 1.14).

## **2.4 Clinical Evidence and Practice Guidelines**

Over the quarter-century history of statins, findings of randomized controlled trials, alone or in combination, provided overwhelmingly strong evidence that statins work equally well across primary and secondary prevention populations,<sup>175</sup> and that their benefits extend to populations that had been historically under-researched such as women,<sup>242</sup> hypertensives,<sup>243</sup> diabetics,<sup>244,245</sup> and individuals with chronic kidney disease.<sup>246</sup> Clinical practice guidelines, and particularly those developed by the NCEP ATP, and most recently ACC/AHA, played an important role in interpreting this evidence and making recommendations for decision makers in clinical practice. The limits of statin therapy have progressively expanded to include individuals at lower risk categories. For instance, although earlier versions of the ATP clinical practice guidelines outlined a moderate strategy for the prevention of coronary heart disease in persons with elevated levels of LDL cholesterol, subsequent versions lowered the threshold for drug treatment, and considerably expanded both the scope and intensity of statin therapy (Table 2.3). (Although the recent ACC/AHA guidelines abandoned LDL cholesterol goals, they continued this trend by recommending statin therapy for individuals at very low risk of developing coronary heart disease.)

For the development of its recommendations, NCEP ATP and ACC/AHA placed primary emphasis on large randomized controlled clinical trials and meta-analyses of large trials. In addition to large trials, however, a series of randomized controlled trials of varying sizes

have yielded a vast body of evidence on the effects of statins, which, to a large extent, were not taken into consideration in clinical practice guidelines.

Some components of the clinical practice guidelines recommendations were controversial. For instance, the ATP guidance to use lipid-lowering drugs in individuals without established coronary heart disease (primary prevention) was ahead of its time – and ahead of the existing evidence. While the evidence on statins for reducing the risk of total mortality remained inconsistent in the peer-reviewed literature, the ATP clinical practice guidelines recommended the use of lipid-lowering drug therapy, and specifically statins, in individuals without established coronary heart disease. In contrast, the latest ACC/AHA guidelines referred to a stronger foundation of randomized controlled trial evidence on this front.<sup>157</sup>

Until recently, the ATP recommendation to use statins in primary prevention was at odds with the debate in the peer-reviewed literature. Authors of meta-analyses and editors of medical journals who published these analyses demanded strong evidence that statins resulted in a survival benefit in the primary prevention setting. Given the lack of such evidence, many remained opposed to the suggestion that individuals without established coronary heart disease should be prescribed statins. The editors of the Archives of Internal Medicine suggested that “statin medications for persons without coronary artery disease [is an example] of the widespread use of medications with known adverse effects despite the absence of data for patient benefit for these indications.”<sup>247</sup> Clinical guideline developers attributed the perceived lack of a robust survival benefit to the relatively low risk of mortality in this patient population and insufficient length of follow-up in randomized controlled trials. The premise of this argument was that lower risk populations might also achieve significant reductions in all-cause mortality if they were treated for longer than those tested in the trials. Prominent cardiologists joined the debate and asked: “can we expect any drug ... to reliably produce a survival benefit in asymptomatic individuals within a few years?”<sup>248</sup> The publication in 2012 of an individual patient-level meta-analysis performed by the Cholesterol Treatment Trialists’ Collaboration confirmed the therapeutic value (and survival benefit) of statin therapy in primary prevention – arguably concluding another chapter of controversy in the history of statins.

**Table 2.3 – LDL Cholesterol Goals and Cut-points for Drug Therapy in Different Risk Categories in NCEP ATP Guidelines.**

ATP Version	Risk Category	LDL Cholesterol Goal mg/dL	Consider Drug Therapy mg/dL
ATP-I	With coronary heart disease or two other risk factors *	<130	≥160
	Without coronary heart disease or two other risk factors *	<160	≥190
ATP-II	With coronary heart disease	≤100	≥130
	Without coronary heart disease and with two or more risk factors **	<130	≥160
	Without coronary heart disease and with fewer than two risk factors **	<160	≥190
ATP-III	With coronary heart disease or coronary heart disease equivalents (10-year risk >20%) †	<100 In the 2004 update, the optional goal for this risk category was <70 mg/dL.	≥100 In the 2004 update, it was recommended to consider drug therapy when patients had a baseline LDL cholesterol level <100 mg/dL.
	Without coronary heart disease and with two or more risk factors (10-year risk 10% to 20%) ‡	<130 In the 2004 update, the optional goal for this risk category was <100 mg/dL.	≥130 In the 2004 update, it was recommended to consider drug therapy when patients had a baseline LDL cholesterol level between 100 and 129 mg/dL.
	Without coronary heart disease and with two or more risk factors (10-year risk <10%) ‡	<130	≥160
	Without coronary heart disease and with 0-1 risk factor ‡	<160	≥190 In the 2004 update, the optional goal for this risk category was <100 mg/dL.

\* Risk factors include male sex, family history of premature coronary heart disease, cigarette smoking, hypertension, low HDL cholesterol, diabetes mellitus, definite cerebrovascular or peripheral vascular disease, or severe obesity.

\*\* Risk factors include male sex ≥45 years of age, female sex ≥55 years of age or premature menopause without estrogen replacement therapy, family history of coronary heart disease, current cigarette smoking, hypertension, low HDL cholesterol, or diabetes mellitus.

† Coronary heart disease equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease, diabetes, and 2+ risk factors with 10-year risk for hard coronary heart disease >20%.

‡ Risk factors include age (men ≥45 years; women ≥55 years), family history of premature coronary heart disease, cigarette smoking, hypertension or low HDL cholesterol.

## 2.5 The Way Forward

Today, an important question that remains unresolved is the extent to which individual statins are different from each other in terms of their effects on clinically meaningful benefit and harm outcomes. Although the latest report of the ACC/AHA recommended that statins should be considered as first-line drugs when LDL cholesterol-lowering drugs are indicated to achieve treatment goals, it provided no specific guidance around which statin should be the preferred option to initiate therapy. Instead, the guidelines suggested that the selection of initial drug therapy would be influenced by the lipoprotein profile and magnitude of change needed to lower the risk of coronary heart disease in individual patients. By doing so, guideline developers assumed that the benefits of statins were entirely attributable to their LDL cholesterol lowering effects – implying that the benefits of individual statins would be equivalent at comparable doses (achieving equivalent relative LDL cholesterol reductions). However, no particular study has adequately<sup>5</sup> evaluated this question.

Six statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) currently marketed in the United States differ in the degree of LDL cholesterol lowering that can be achieved per mg dose. With the basic mechanism of cholesterol lowering remaining the same, the six statins differ to a various extent in pharmacological properties and it would be expected that they differ in terms of their clinical efficacy. Whether – and to what extent – individual statins at comparable doses (with similar LDL cholesterol lowering effects) would be different from each other in terms of their effect on clinical endpoints, total mortality, and harmful side effects forms the basis of the empirical work that is reported in the next chapters of this thesis. This question has not been addressed in a comprehensive manner in previous meta-analyses. Although a seventh statin, pitavastatin (marketed as Livalo®), has recently been launched in the United States, this product is not included in the empirical work presented in this thesis because of its recent launch date of 2009.

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<sup>5</sup> Previous meta-analyses that evaluated the comparative benefits and harms of different statins are reviewed in Chapter 5 (*Comparative Benefits of Individual Statins*) and Chapter 6 (*Comparative Harms of Individual Statins*). The main limitation of these studies is that they were based on placebo-controlled trials, without taking into account the findings of head-to-head trials, which resulted in an enormous loss of valuable data.

## Chapter 3

### Evidence Review and Synthesis Methods

Evidence review and synthesis approaches such as systematic reviews and meta-analyses have a clear role in ensuring that healthcare interventions are based on complete and up to date evidence. As individual studies rarely provide definitive answers to clinical effectiveness and safety questions, systematic reviews are pivotal in piecing together the available evidence from a multitude of sources and making obvious the gap between what is known about a given question and what decision makers need to know to make informed decisions.<sup>28</sup> Clinical practice guidelines increasingly use systematic reviews of existing evidence to develop their recommendations.

Meta-analyses are statistical tools for combining the results of several comparable studies identified in a systematic review to summarize available evidence into a pooled estimate for the outcome of interest.<sup>249</sup> They increase the overall sample size (thus power) of the analysis, relative to any single trial, providing a more precise estimate of treatment effect. They are useful in explaining differences between results of individual studies and can provide for pre-planned, transparent, proven methods to minimize bias. Relatively new meta-analytic approaches such as network meta-analyses also allow for the simultaneous comparison of multiple treatments in an internally coherent analysis.<sup>250</sup>

Weighing the relative value of waiting for comparative evidence from future prospectively designed studies or making decisions based on the existing evidence base, an efficient strategy is to initially prioritize the review and synthesis of the existing body of evidence on statins. As reviewed in the previous chapter (Chapter 2: *Evolution of Clinical Evidence: The Case of Statins*), a large number of randomized controlled trials of varying sizes evaluated the benefits and harms of statins over the past 25 years. Hundreds of thousands of individuals with or without coronary heart disease participated in hundreds of statin trials conducted in several countries around the world. Although a large number of these trials were placebo-controlled, a considerable number of active-comparator (head-to-head) trials explored the comparative benefits and harms of individual statins at different doses. This

large body of placebo-controlled and active-comparator trial evidence provides an opportunity to perform a comparative assessment of individual statins.

The empirical work presented in this thesis is grounded on a systematic review and meta-analysis of the randomized trial literature on statins. The objective of the systematic review was to comprehensively identify the randomized controlled trial evidence on statins based on pre-determined identification and selection criteria. The comparative benefits and harms of statins were explored using relatively novel evidence synthesis approaches called network meta-analyses. This chapter provides an overview of these evidence review and synthesis methods.

### **3.1 Rationale for a systematic approach**

Systematic reviews are methods to *systematically* assemble and synthesize evidence from multiple sources on the effectiveness – and increasingly, comparative effectiveness – of interventions. As defined by the Cochrane Collaboration:

A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review.<sup>251</sup>

In the era of evidence-based medicine, systematic reviews offer a powerful solution to finding, evaluating, and incorporating new research knowledge into everyday clinical decision-making. Systematic reviews allow researchers and health care decision makers to interpret the evidence, to summarize what is known, and to describe the extent to which the evidence is applicable to individual patients seen in clinical practice.<sup>28</sup> Only after a systematic review and synthesis of the existing evidence is one in a position to plan and identify what form of further evidence is required.

Systematic reviews adopt a methodological approach to ensure that evidence is identified, selected, and reviewed in accordance with a protocol.<sup>251</sup> Well-conducted systematic reviews are reproducible as they follow a comprehensive review protocol that outlines the detailed approach to conducting all parts of the literature review. Conducted in a transparent and methodological way, systematic reviews offer a less biased alternative to narrative reviews, which lack an explicit description of systematic methods of searching for, identifying, and including studies.<sup>93</sup> As a result, narrative reviews are criticized on the grounds that they are largely based on a biased citation of studies.<sup>252</sup> Given the clear advantages of systematic reviews over any other type of evidence review strategy, the empirical work presented in this thesis is based on a systematic review of the existing statin evidence base.

## 3.2 Systematic Review Methods

At the outset of the systematic review undertaken for this thesis, a protocol describing the objectives and methods of the systematic review and statistical analysis was developed and subsequently made publicly available on the London School of Economics & Political Science website.<sup>253</sup> This protocol was developed to ensure that evidence was identified, selected, and reviewed properly and based on pre-specified criteria.<sup>6</sup> The protocol focused on the specific purpose of the review, the comparison groups of interest, the sources and search methods used to find evidence, explicit study selection (i.e. inclusion and exclusion strategy) and categorization criteria (i.e. primary and secondary prevention of coronary heart disease), the variables to be captured during data extraction, and statistical methods for performing network meta-analyses, including pre-specified sensitivity analyses. The protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews, University of York). The PROSPERO registration number for this systematic review was 2011-CRD42011001470. Deviations from the original protocol are outlined in a later section of this chapter, sub-titled: '*Deviations from Protocol*.'

### 3.2.1 Identification and Selection of Studies

A systematic review was performed based on the most up-to-date Centre for Reviews and Dissemination (CRD) guidelines.<sup>254</sup> Instead of performing an 'umbrella' review of the existing systematic reviews of statins, a new search strategy was developed to comprehensively identify the active-comparator trials that were not included in previous meta-analyses of placebo-controlled trials. Search terms were pre-defined, and searches were conducted in MEDLINE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. These electronic databases were searched starting from January 1, 1985 (approximately five years before the first statin was available on the market) until January 1, 2011. The actual search date was January 3, 2011.

The electronic search strategy was devised with the assistance of an information specialist at the London School of Economics & Political Science Library in order to ensure that an efficient search string was developed. The search strategy employed terms for both the drug and therapeutic indication. The following terms were used: *atorvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, cholesterol, cardiovascular disease, and Hydroxymethylglutaryl-CoA Reductase Inhibitors/therapeutic use*. The search strategy also included limits to ensure that the identified articles were randomized trials performed in humans and published after 1985. In addition to the searches in electronic databases, a manual search was performed using personal reference files and reference lists from

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<sup>6</sup> A copy of the protocol is included in the *Appendix*.

original communications and review articles. The list of identified qualitative and quantitative systematic reviews (meta-analyses) was manually reviewed to cross check references and confirm the comprehensiveness of study identification and selection.

The review was limited to randomized controlled clinical trials. Randomization is the only way to prevent systematic differences between baseline characteristics of participants in different intervention groups in terms of both known and unknown (or unmeasured) confounders.<sup>255</sup> In the absence of randomization, a large number of selection biases can render the results of clinical trials invalid. Empirical evidence suggests that, on average, non-randomized studies produce effect estimates that indicate more or less extreme benefits of the effects of health care than randomized trials.<sup>256,257</sup> However, the magnitude and even the direction of these biases are difficult to predict. Although there are methodologies that would partly take into account potential biases in evidence review and synthesis,<sup>258</sup> the research community has not reached a consensus around the relative validity of randomized and non-randomized studies;<sup>256,259-261</sup> and hence the appropriateness of making decisions on the basis of non-randomized studies. Accordingly, identifying non-randomized studies of statins was beyond the scope of the current systematic literature review.

The focus of the review was on coronary heart disease. According to the existing clinical practice guidelines,<sup>154</sup> statins are indicated for the primary and secondary prevention of coronary heart disease. Given the common co-morbidity profile of individuals with, or at risk of developing, coronary heart disease, patient populations with diverse risk profiles (and co-morbidities) were eligible for inclusion. For instance, patients with diabetes and hypertension can greatly benefit from statin therapy. In fact, diabetes is considered as a coronary heart disease risk equivalent, and a large number of diabetic individuals receive statin therapy. However, a decision was made *a priori* that trials including patient populations with chronic kidney disease were not eligible for inclusion. This was because individuals with chronic kidney disease have non-traditional risk factors such as anemia and factors favoring vascular calcification, which may complicate the interpretation of the findings in regards to the comparative benefits and harms of statins in these populations.<sup>262</sup>

Studies with particularly short follow-up durations (<4 weeks) were excluded with the rationale that clinical benefits of statins would not be apparent during such a short time period. To be eligible for inclusion, trials had to have at least 50 individuals included in every arm of the trial. This decision was made on two grounds. First, the objective was to ensure that there would be a sufficient sample size to observe rare clinical events. Second, trials with fewer than 50 individuals per treatment arm may not be methodologically rigorous. Randomization rests on the principle that treatment arms at baseline are balanced

on potentially confounding factors. This is often not possible in small trials with fewer than 50 individuals per trial arm.<sup>263,264</sup>

The identified set of titles and abstracts were reviewed in two levels. The first-level screening was a review of the titles and abstracts according to the exclusion criteria. The full-text copies of the studies that were still deemed to be relevant following the first-level screening were then obtained, and these full-text articles were reviewed in detail according to the inclusion criteria. According to the CRD Systematic Review Guidelines, two researchers<sup>7</sup> independently performed abstract, title, and full-text screening, and one researcher was responsible for the final selection for each study. Given that this systematic review of the literature was undertaken specifically for this dissertation, as the principle researcher, I was responsible for all aspects of the systematic review including study identification and selection.

#### 3.2.1.1 *Exclusion Criteria*

The following exclusion criteria were applied to the titles and abstracts identified in each of the searches (first-level screening):

- Quasi-randomized trials or non-randomized publications (i.e. strong quasi-experimental designs such as interrupted time-series analyses, and weak observational designs such as case reports, cohort studies and case-control studies)
- Studies evaluating treatment options other than statins
- Studies of multi-interventional therapies where the effect of the statin could not be separated out (i.e. studies were excluded if at least two arms of the randomized trial did not report findings for the interventions of interest)
- Review articles<sup>8</sup>
- *in vitro* or animal studies
- Studies in populations other than primary and secondary prevention of coronary heart disease
- Studies in pediatric populations (i.e. individuals who were less than 18 years old)
- Studies with particularly short follow-up durations (<4 weeks)
- Studies with no treatment arms having more than 50 patients

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<sup>7</sup> Another researcher provided assistance (worked in parallel) for this task.

<sup>8</sup> Review articles were excluded but filed for subsequent manual cross-checking of reference lists. Of particular interest were meta-analyses.

### 3.2.1.2 *Inclusion Criteria*

The following inclusion criteria were applied to the full-text articles (second-level screening):

- Randomized, controlled trials (randomized, prospective, controlled design); both open-label and double-blind designs were included
- Patients in at least one arm of the trial received atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin (either generic or brand-name formulations)
- The patients of interest were patients who were at least 18 years of age with, or at risk of developing, coronary heart disease (secondary or primary prevention populations, respectively)
- Studies had to report detailed dosing regimens received by patients on all comparator arms
  - To be included, studies had to report whether they employed fixed or variable dosing regimens. Similarly, average study-level dose of treatment received over the course of the trial had to be reported
- To be included in the statistical analysis, each selected study had to report surrogate endpoints (e.g. reductions in cholesterol concentrations), clinical events (e.g. reductions in the risk of total mortality, or the risk of developing coronary or cerebrovascular events), tolerability (e.g., discontinuations due to adverse events), or primary and secondary harm endpoints of interest (e.g., myalgia, liver transaminase elevations, creatine kinase elevations, incident cancers and diabetes, and rhabdomyolysis). The specific outcomes of interest are also listed below.

Trials with crossover designs (where patients changed arms) were included only if results were available from the first randomized controlled period. Studies that compared multiple doses of the same statin were included. Finally, both fixed-dose and titration trials were eligible for inclusion.

The inclusion and exclusion processes were carefully documented, including completion of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart<sup>265</sup> as reported in Chapters 4-7.

### 3.2.1.3 *Trial Categorization*

Whenever possible, the included trials were categorized as primary prevention, secondary prevention, or mixed patient population. Primary prevention trials were those that assessed the efficacy and safety of statins in patients free of coronary heart disease at baseline. Secondary prevention trials were those that evaluated statins in patients with established coronary disease (i.e. often following a myocardial infarction). Given that a number of trials included a combination of both primary and secondary prevention populations, these trials were categorized as having a mixed patient population. In cases where study authors reported data separately on a sole primary prevention or secondary prevention group within a mixed trial, this information was recorded separately for use in respective statistical analyses.

Although the risk cut-off between primary and secondary prevention populations may not be fully justified on the basis of slippery definitions between primary and secondary prevention,<sup>237</sup> literature commonly refers to individuals as either primary or secondary prevention. Therefore, such a categorization was adopted in this review. Trials that included at least 80% of participants with established coronary heart disease or reported data separately on a sole secondary prevention group were categorized as secondary prevention trials. Similarly, trials that included at least 80% of participants without established cardiovascular disease or reported data separately on a sole primary prevention group were categorized as primary prevention. All remaining trials were categorized as having a mixed patient population.

### 3.2.3 *Data Extraction*

A structured data-extraction form implemented in Microsoft Excel was used to ensure consistency of data extraction for each study. Data on the following items were extracted:

#### 3.2.3.1 *Study-level Characteristics*

- Trial (trial reference)
- Population severity (narrative description of cardiovascular risk factors of the patient population)
- Patient population (primary prevention, secondary prevention, or mixed population)
- Dosing regimen (fixed-dose or titration trial)
- Co-morbid conditions (condition of primary interest was diabetes)

- Concomitant medication usage
- Trial duration in weeks
- Follow-up duration in weeks (time point at which outcomes were reported)
- Primary statin and dosage
- Comparator(s) and dosage(s) (these could be other statin treatments, placebo, usual care, or no treatment)
- Number of patients in each study arm (number randomized to each study arm)

#### 3.2.3.2 *Surrogate Endpoints*

- Mean reduction in LDL cholesterol concentration from baseline
- Mean reduction in HDL cholesterol concentration from baseline
- Mean reduction in Total cholesterol concentration from baseline

The following data elements were extracted for LDL, HDL, and Total cholesterol endpoints:

- Mean concentration (and its standard deviation or variance) at baseline for all treatment arms
- Mean concentration (and its standard deviation or variance) at follow-up for all treatment arms
- Alternatively, if available, mean difference between treatment arms (and standard deviation or variance of the difference) of the mean reduction in concentration from baseline

#### 3.2.3.3 *Clinical Benefit Endpoints*

- Number of all-cause deaths (all-cause mortality or total mortality), for which the following data elements were extracted:
  - Number of deaths due to any reason in all treatment arms
  - Number of individuals randomized to all treatment arms
- Number of major coronary events (composite of major coronary events were defined as deaths from coronary heart disease and non-fatal myocardial infarctions), for which the following data elements were extracted:

- Number of individuals with coronary heart disease deaths in all treatment arms
- Number of individuals with non-fatal myocardial infarctions in all treatment arms
- Alternatively, if this information was available, the number of individuals with major coronary events in all treatment arms
- Number of individuals randomized to all treatment arms
- Number of major cerebrovascular events (composite of fatal- and non-fatal strokes and transient ischemic attacks), for which the following data elements were extracted:
  - Number of individuals with fatal strokes in all treatment arms
  - Number of individuals with non-fatal strokes in all treatment arms
  - Number of individuals with transient ischemic attacks in all treatment arms
  - Alternatively, if this information was available, the number of individuals with major cerebrovascular events in all treatment arms
  - Number of individuals randomized to all treatment arms

#### 3.2.3.4 *Clinical Harm and Tolerability Endpoints*

- Number of trial withdrawals due to adverse events (discontinuations due to adverse events), for which the following data elements were extracted:
  - Number of discontinuations due to adverse events in all treatment arms
  - Number of individuals randomized to all treatment arms
- Number of individuals experiencing clinically meaningful transaminase elevations from baseline levels (three times or higher than baseline values, as commonly defined by trial investigators) (composite of two hepatic transaminases: aspartate transaminase [AST] and alanine transaminase [ALT]), for which the following data elements were extracted:
  - Number of individuals with clinically meaningful elevations in baseline aspartate transaminase concentrations in all treatment arms
  - Number of individuals with clinically meaningful elevations in baseline alanine transaminase concentrations all treatment arms

- Alternatively, if this information was available, the number of individuals with clinically meaningful hepatic transaminase elevations in all treatment arms
  - Number of individuals randomized to all treatment arms
- Number of individuals experiencing clinically meaningful elevations in baseline creatine kinase concentrations (as defined by trial investigators, ranging from three to 10 times higher than baseline levels), for which the following data elements were extracted:
  - Number of trial participants with clinically meaningful creatine kinase elevations in all treatment arms
  - Number of individuals randomized to all treatment arms
- Number of individuals with incident cancers, for which the following data elements were extracted:
  - Number of individuals with incident cancers in all treatment arms
  - Number of individuals randomized to all treatment arms
- Number of individuals with incident diabetes, for which the following data elements were extracted:
  - Number of individuals with incident diabetes in all treatment arms
  - Number of individuals randomized to all treatment arms
- Number of individuals with rhabdomyolysis, for which the following data elements were extracted:
  - Number of individuals with rhabdomyolysis in all treatment arms
  - Number of individuals randomized to all treatment arms

### 3.2.3.5 *Methodological Quality of Included Studies*

- Trial participant and investigator blinding
  - Question asked was: “did the investigators blind trial participants and researchers from knowledge of which treatment a trial participant received?”
- Random sequence generation

- Question asked was: “were the methods for allocation sequence reported to determine whether it produced comparable groups?”
- Allocation concealment
  - Question asked was: “were the methods used to conceal the allocation sequence reported to determine whether group allocations could have been foreseen before or during treatment initiation?”
- Blinding of outcome assessment
  - Question asked was: “did trial investigators blind outcome assessment from knowledge of which intervention a participant received?”
- Indications of incomplete outcome data
  - Question asked was: “did the investigators report completeness of outcome data for LDL cholesterol lowering, including attrition and exclusions from the analysis?”
- Indications of selective reporting
  - Primary question asked was: “did the investigators fail to report tolerability and harm outcomes commonly reported in randomized trials of statins [e.g., withdrawals due to adverse events, creatine kinase elevations, hepatic transaminase elevations, or myalgia]?”
  - Secondary question asked was: “were there deviations in trial outcomes from published protocols (in cases where trial protocols were available)?”

#### 3.2.3.6 *Funding Source*

- Industry (any private for-profit pharmaceutical company involved in research and development, manufacturing, or marketing of statins)
- Governmental agency or department
- Non-governmental organization
- Academic institution/teaching hospital
  - In cases where trial funding source was not clearly reported, trial author affiliations were checked and studies with industry-affiliated authors were categorized as industry-sponsored. Also, trials with industry, government, and/or academic institution co-sponsorship were categorized as industry-

sponsored (unless the trial investigators included a statement suggesting that the funding body had no involvement in trial design, conduct, analysis or reporting).

Once the included list of studies was finalized, data extraction was performed by one researcher for all identified studies. Per the CRD Systematic Review Guidelines, another researcher checked the quality of the completed data extraction sheets for consistency and accuracy. Discrepancies were settled through consensus discussion. To ensure the quality of extraction, the consistency of extracted data (in its entirety) was cross-checked with data used in previously published meta-analyses. In addition to primary data extraction, whenever possible, data from published reviews were used when study authors of previous meta-analyses contacted trial investigators and requested unpublished information on outcomes of interest.

### **3.3 Statistical Analysis Methods**

The primary objective of the statistical analysis was to quantitatively synthesize the total body of the randomized controlled trial evidence on statins as identified by the systematic review of the literature. More specifically, the objective was two-fold: first, to quantify the comparative effects of individual statins at different doses on cholesterol levels (surrogate endpoints), and second, to quantify the comparative benefits and harms of individual statins in terms of their effect on total mortality, major coronary events, and major cerebrovascular events (clinical benefit endpoints), and on discontinuations due to adverse events, myalgia, hepatic transaminase elevations, and creatine kinase elevations, in addition to cancer, diabetes, and rhabdomyolysis (clinical harm endpoints).

First, the included trials were qualitatively summarized, describing the types of comparisons and important clinical and methodological variables (such as trial population, year of publication, mean age of patients, and risk of cardiovascular disease). Statistical analyses were subsequently performed separately for each endpoint of interest:

- Surrogate endpoints
  - LDL cholesterol reduction from baseline
  - HDL cholesterol reduction from baseline
  - Total cholesterol reduction from baseline
- Clinical benefit endpoints
  - All-cause mortality

- Major coronary events
- Major cerebrovascular events
- Tolerability and harm endpoints
  - Discontinuation due to adverse events
  - Myalgia occurrence
  - Hepatic transaminase elevation
  - Creatine kinase elevation
  - Incident cancer
  - Incident diabetes

Statistical analyses included traditional pair-wise meta-analyses and network meta-analyses. All statistical analyses were based on the total number of randomly assigned participants, irrespective of how study authors reported the results. The approach taken to perform the statistical analyses is outlined in detail below.

### 3.3.1 *Traditional Pair-wise Meta-analysis*

First, traditional pair-wise meta-analyses were performed to synthesize studies that compared the same two interventions (e.g. trial of atorvastatin vs. placebo was pooled with other trials of atorvastatin vs. placebo). Traditional pair-wise meta-analysis is a statistical tool for pooling the results of multiple comparable trials that directly compare the same two interventions.<sup>266</sup> By increasing the overall sample size of the analysis (therefore power), traditional pair-wise meta-analysis provides a more precise estimate of a treatment effect, which is of considerable importance to make inferences on a large body of evidence such as the one for the statin literature.<sup>93,267,268</sup> As reviewed in the previous chapter, a large number of meta-analyses have already been conducted to synthesize the evidence on statins and address important questions that had remained unanswered in individual trials.

The main consideration when performing and interpreting traditional pair-wise meta-analyses is similarity (also termed homogeneity) across the pooled set of studies in terms of trial and patient population characteristics. If the set of trials are not adequately homogenous (i.e., there is considerable between-study heterogeneity), the relevance of the pooled findings from traditional pair-wise meta-analysis to the specific target population becomes less certain.<sup>269</sup> However, when heterogeneity exists, meta-analyses could be useful in exploring how treatment effects vary across subgroups (e.g., age and sex) and study settings on the basis of sub-group analyses and meta-regressions.<sup>249</sup>

The objective of performing traditional pair-wise meta-analyses was three-fold. The first objective was to pool all statin trials together and quantify the benefits of statins as a drug class in comparison to control treatment, which has previously been done, as referenced in Chapter 2 of this thesis, entitled: *“Evolution of Clinical Evidence: The Case of Statins.”* However, an attempt was made to update the previous pair-wise meta-analyses to reflect the changing nature of randomized controlled trial evidence base of statins. The second objective was to statistically summarize all direct head-to-head comparisons of statins, which has not been performed in previous meta-analyses. Pair-wise meta-analyses of all available direct comparisons (first between statins and control, and second among individual statins) constituted the building blocks of subsequent network meta-analyses. The direction and magnitude of relative treatment effects observed in pair-wise meta-analyses of direct comparisons are often used to gauge important assumptions of network meta-analyses. Indeed, the third objective was to compare and contrast (and quality check) the findings of the network meta-analyses to those obtained from pair-wise meta-analyses. This cross checking is particularly important to ensure the consistency of the findings from different analyses. (Assumptions of network meta-analyses are discussed later in this chapter.)

The approach to perform traditional pair-wise meta-analyses is described in Box 3.1. For each pair-wise comparison between statins, the relative effect (in terms of odds ratios) was calculated with a 95% confidence interval using two separate approaches. First, fixed-effect analyses were performed using the Mantel-Haenszel method.<sup>270</sup> Second, random-effects analyses were performed using the DerSimonian Laird method.<sup>271</sup> Fixed- and random-effects approaches relate to the concept of heterogeneity and are critical in traditional pair-wise meta-analyses. Heterogeneity – or more accurately, between-study heterogeneity – results from systematic differences in (average) patient or study characteristics across trials, which influence the true relative treatment effect and result in systematic differences in the effect sizes across trials. The fixed-effect method assumes that every trial has an identical treatment effect, suggesting that there is no heterogeneity across the identified set of trials.<sup>272</sup> This is equivalent to making the strong assumption that the trials are identical in every aspect of design and implementation, including the patient population characteristics.<sup>273</sup> The random-effects model makes a more conservative assumption in that it takes into account potential heterogeneity by assuming that each treatment effect is drawn from a common distribution, whose mean and variance are estimated from the data.<sup>274</sup>

### Box 3.1: Analytical Approach for Traditional Meta-analysis

In the traditional pair-wise meta-analysis with a number of trials comparing the same set of two interventions 1 and 2, the relative treatment effect between these interventions is denoted as  $d_{12}$ . In the fixed-effect model, each study  $i$  provides an estimate of the same parameter  $d_{12}$ , with sampling error. In the random-effects model, the study level treatment effect from each study  $i$  is obtained from a common distribution with mean  $d_{12}$  and variance  $\sigma^2_{12}$ . This common distribution is denoted as:

$$\delta_{i,12} \sim N(d_{12}, \sigma^2_{12})$$

The fixed-effect model can be obtained by setting the variance to zero.

For binary outcomes, a binomial likelihood is used:

$$r_{ik} \sim \text{Binomial}(p_{ik}, n_{ik})$$

where  $r_{ik}$  is the number of events in arm  $k$  of trial  $i$ ,  $n_{ik}$  is the total number of individuals in arm  $k$  of trial  $i$ , and  $p_{ik}$  is the probability of an event in arm  $k$  of trial  $i$

The model is then specified as:

$$\text{logit}(p_{ik}) = \mu_i + \delta_{i,12}I_{(k \neq 1)}$$

Where  $I_{(u)} = 1$  if  $u$  is true, and 0 otherwise.

The model can be written for a random-effects specification:

$$\text{logit}(p_{i1}) = \mu_i$$

$$\text{logit}(p_{i2}) = \mu_i + \delta_{i,12}$$

The model can also be written for a fixed-effect specification:

$$\text{logit}(p_{ik}) = \mu_i + d_{12}I_{(k \neq 1)}$$

where  $\mu_i$  are trial-specific baselines (log-odds of the outcome in the control treatment) and  $\delta_{i,12}$  are the trial-specific log-odds ratios of events on the active comparator group compared to control, where the random-effects for the trial-specific log-odds ratios come from a common distribution:  $\delta_{i,12} \sim N(d_{12}, \sigma^2_{12})$ .

For continuous outcomes, a normal likelihood is used:

$$y_{ik} \sim N(\theta_{ik}, \text{se}^2_{ik})$$

where  $y_{ik}$  is the mean change from baseline in arm  $k$  of trial  $i$ , and standard error  $\text{se}^2_{ik}$  in arm

$k$  of trial  $i$ . The parameter of interest is the mean  $\theta_{ik}$ , which can be specified on the natural scale as:

$$\theta_{ik} = \mu_i + \delta_{i,bk}I_{(k \neq 1)}$$

Fixed- and random-effect specifications for the normal likelihood model are as described for the binomial likelihood model.

In terms of fixed- versus random-effects models, guidance around which method to adopt in traditional pair-wise meta-analyses varies in the literature. For instance, Borenstein and colleagues favor an approach whereby the decision to use fixed- vs. random-effects models are determined *a priori*.<sup>273</sup> Others suggest that both models should be adopted subsequently and the sensitivity of the findings to different models should be reported.<sup>251</sup> From a statistical standpoint, it should be noted that both models yield identical results if there is no heterogeneity (this is to say that the random-effects model is reduced to the fixed-effect equivalent when there is no between-study heterogeneity). Therefore, the more conservative approach is to adopt a random-effects model with the reasonable expectation that *some* heterogeneity may be present across the identified set of trials, and that this heterogeneity should be taken into account when interpreting the uncertainty around the pooled treatment effect estimate.<sup>251</sup> With this rationale, all base-case analyses reported in this thesis are based on random-effects models (one exception is presented in Chapter 7: *Methodological Quality and Risk of Bias in Randomized Controlled Trials of Statins*).

In addition to considerations in regards to the fixed- versus random-effects assumption, the potential heterogeneity was investigated both qualitatively and quantitatively. First, the forest plots of the relative treatment effects from the individual trials and pair-wise meta-analyses were visually inspected to search for groups and outliers. This was statistically supplemented by using the  $I^2$  measure, which estimates the percentage of total variation among studies that can be considered to be due to heterogeneity.<sup>275</sup> In line with the Cochrane Collaboration recommendations, rough thresholds of 25%, 50%, and 75% were used to define low, moderate, and high heterogeneity.<sup>251</sup> Moderate and high heterogeneity were investigated by inspecting trial-level variables that could potentially explain the observed differences. These included baseline mean age, baseline LDL cholesterol concentration, and trial publication year, which are discussed in more detail later in this chapter. Finally, small-study effects were investigated using contour-enhanced funnel plots.<sup>276</sup> All traditional meta-analysis models were implemented in Stata version 11.0 (StataCorp LP, College Station, Texas, United States).

### 3.3.2 *Network Meta-analysis*

Pair-wise meta-analyses have important limitations. First, in conditions with several drug options, pair-wise meta-analysis is limited by the relatively small number of trials (or the lack of trials) that directly compare a particular pair of drugs. By definition, pair-wise meta-analysis is incapable of comparing multiple active comparators simultaneously. Second, when there are multiple drugs, performing separate pair-wise meta-analyses for each comparison becomes impractical (or impossible if there are no trials that include the comparison of interest). Third, focusing on two drugs at a time, such an approach also does not adequately take into account the between-trial variance structure in multi-arm trials.<sup>277,278</sup>

To address these limitations of pair-wise meta-analyses, network meta-analyses were conducted to determine the comparative effects of individual statins. Network meta-analysis is a relatively new method to allow for the simultaneous comparison of multiple interventions. Although these approaches can be considered as a generalization of traditional pair-wise meta-analyses, they are different in several important aspects. For instance, in addition to analyzing the direct within-trial comparisons between two drugs (B vs. A), the network meta-analysis framework enables the incorporation of indirect comparisons constructed from trials that have one drug in common – also called a common comparator (B vs. A and C vs. A, where A is a common comparator).<sup>95</sup> In this framework, direct evidence refers to evidence from trials that include a specific pair-wise comparison whereas indirect evidence refers to evidence obtained from a network of trials that do not include that particular comparison. In the absence of trials involving a direct comparison of interventions, an indirect comparison provides useful evidence for the relative treatment effects between competing interventions.<sup>98,279</sup>

#### 3.3.2.1 *Combining Direct and Indirect Evidence in Network Meta-analyses*

The Cochrane Collaboration recommends that, in situations where both direct and indirect evidence are available, the two types of evidence should be considered separately.<sup>251</sup> To quote Caldwell and colleagues: “difficulties arise, however, if the direct evidence is inconclusive but the indirect evidence, either alone or in combination with the direct evidence, is not”.<sup>95</sup> Furthermore, considering direct and indirect evidence in isolation from each other becomes increasingly impractical as the number of treatments increases. From a decision-making standpoint, it is particularly difficult to assess the relative effect of multiple drugs in the form of disparate pair-wise meta-analyses on direct and indirect comparisons so combining direct and indirect evidence has clear appeal.

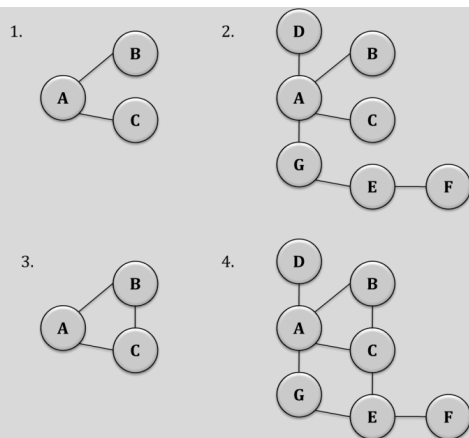
By integrating both direct and indirect evidence, network meta-analyses of existing evidence are capable of comparing all relevant treatments in an evidence network. This approach has potential advantages even when direct comparisons between interventions of interest exist. For instance, an indirect comparison may be less biased than the findings of an individual trial that directly compares the interventions.<sup>280,281</sup> Even when the results of the direct evidence are unbiased and conclusive, combining direct estimates with the results of indirect comparisons in a network meta-analysis may result in more refined estimates by considering a broader evidence base.<sup>257</sup> In general, if the available evidence base consists of a network of connected multiple randomized trials involving treatments compared directly, indirectly, or both, the entire evidence base of randomized trials can be synthesized in an internally coherent analysis.<sup>282</sup>

Box 3.2 below provides a brief overview of different evidence network structures.

### **Box 3.2: Networks of Randomized Trials**

The schematic below shows a number of evidence networks of varying complexity. In each network diagram, each node shows a treatment and the connecting lines indicate one or more direct pair-wise comparison(s) (direct head-to-head trial) between two treatments. For every treatment in a connected network, a relative treatment effect can be estimated as compared to another treatment in the network.

In the first diagram, treatments B and C have not been trialed against each other, but both have a trial against treatment A (common comparator). In this case, an indirect comparison can provide the relative treatment effect between treatments B and C using treatment A as a common comparator. In the second network diagram, not all treatments have a common comparator but all treatments are still connected in a network so relative treatment effects can be obtained for all comparisons of interest. Both of these evidence structures are referred to as indirect treatment comparisons.



*\* This figure was adapted from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons Report Part II developed by Jansen and colleagues.<sup>283</sup>*

In the third network diagram, there is direct evidence on the comparison between treatments B and C, in addition to indirect evidence through treatment A, creating a 'closed loop' (each comparison has both direct and indirect evidence). This evidence structure with a closed loop is often referred to as a mixed treatment comparison. The fourth network diagram is more complex as it has two closed loops. Whatever the complexity of the network structure, relative effects can be obtained on all comparisons of interest in the treatment network. Collectively, evidence structures that contain a closed network of comparisons (of open or closed loops) are referred to as network meta-analyses. For the sake of simplicity, all indirect comparisons (with or without closed loops) are referred to as network meta-analyses in this thesis.

As described in Box 3.2, network meta-analysis can either have a single indirect comparison between two drugs or can include two or more drugs being compared indirectly with at least one pair of drugs compared both directly and indirectly. The latest statistical methods facilitate the incorporation of direct and indirect evidence in any network structure and complexity, as long as treatments are connected in a network.<sup>283-285</sup>

An important consideration when using indirect evidence is that the uncertainty in an indirect comparison is always greater than the uncertainty in the direct comparisons from which it is composed. This is particularly important when more than a few links separate two drugs of interest in an evidence network (as an example, consider the comparison between treatments D and E in the second network diagram in Box 3.2). In such cases, an indirect comparison may not provide a precise estimate of relative effect because each link tends to increase the uncertainty of the indirect comparison.<sup>286</sup> However, if both direct and

indirect evidence is available, indirect evidence carries less weight in the analysis (but continues to contribute information to the analysis). Also, the more distant the indirect evidence from the comparison of interest, the lower the weight attached to it in the analysis as a function of its greater variance.<sup>286</sup>

Notably, by combining relative treatment effects from randomized controlled trials, network meta-analysis preserves the within-trial randomized treatment comparison of each trial while combining all available comparisons between treatments.<sup>283</sup> This is important since a naïve comparison that does not maintain randomization (by comparing effects observed in single trial-arms) would create an observational study with groups that may not be comparable on potential confounding factors.<sup>287</sup>

While randomization is preserved within trials in network meta-analyses, it does not hold across trials. Therefore, differences across trials that are relative treatment effect modifiers may result in biased estimates of comparative treatment effect.<sup>288</sup> Examples of key relative treatment effect modifiers include differences in patient populations across trials, such as patient age and disease severity. Although some case studies have suggested that indirect comparisons have resulted in invalid estimates of comparative efficacy and safety,<sup>289,290</sup> biased findings were primarily due to flaws in the systematic review methodology, particularly the “lumping together” of different treatment doses or combinations (Box 3.3).<sup>291,292</sup> The validity of the statistical methods underlying network meta-analysis is widely accepted<sup>283,284</sup> and these types of analyses are increasingly appearing in high-impact general medical journals but there is still criticism of this method.<sup>88,89,293-299</sup> Criticisms of the network meta-analysis approach are discussed in Box 3.3.

### **Box 3.3: Criticism and Enthusiasm for Network Meta-analysis**

Over the past decade, researchers raised concerns about combining direct and indirect evidence in network meta-analysis. These concerns primarily focused on the potential (in)validity of indirect comparisons.<sup>300</sup> According to Georgia Salanti: “The criticism and enthusiasm for network meta-analysis echo those that greeted the advent of simple meta-analysis.”<sup>250</sup>

In a landmark study published in 2003, Song and colleagues reviewed the literature on the use of indirect comparisons.<sup>289</sup> According to this review, there was moderate agreement between direct and indirect evidence on the basis of 44 comparisons available from a wide range of medical topics, with three comparisons showing statistically significant discrepancy between the direct and indirect estimates. A closer examination suggested that the observed discrepancies were primarily explained by inappropriate “lumping together” of various treatments at different doses. Although there was no significant

disagreement between different sources of evidence for the majority of comparisons in the literature, the authors concluded that indirect comparison may provide useful or supplementary information on the comparative effectiveness of treatments only when there is no or insufficient direct evidence from randomized trials.<sup>289</sup> In a recent update of their review in 2011, Song and colleagues found that 16 out of 112 trial networks had statistically detectable discrepancy between direct and indirect evidence, concluding: “inconsistency between direct and indirect comparisons may be more prevalent than previously observed.”<sup>290</sup> As in their previous review, however, the observed discrepancy likely reflected the reliability of the identified systematic reviews rather than the indirect comparisons<sup>301</sup> (as has been argued in numerous methodological guidance articles, the validity of indirect comparisons depends on their proper use: meta-analytic approaches – with or without indirect comparisons – can only be as good as the existing pool of randomized trials).<sup>95,282,302,303</sup>

In a separate study, Song and colleagues also surveyed the published literature to identify and document the methodological limitations in the use of indirect comparisons in systematic reviews.<sup>292</sup> They found that six studies published between 2000 and 2007 used naïve indirect comparisons without a common control group. As mentioned previously, these simplistic approaches that informally compare arm-level estimates have clear methodological flaws, and are duly criticized.<sup>304,305</sup> This review also showed that approximately one fifth of 88 identified reviews used advanced methods similar to those used in this doctoral thesis.

Song and colleagues concluded that the main methodological problems in the use of indirect comparisons stemmed from an unclear understanding of underlying assumptions, which resulted in the use of inappropriate methods, and inadequate assessment of consistency between direct and indirect evidence.<sup>292</sup> A recent meta-epidemiological review confirmed that key methodological recommendations for conducting and reporting systematic reviews were not followed in the vast majority of network meta-analyses published in high-impact medical journals.<sup>306</sup>

The *Ad Hoc* Network Meta-analysis Methods Meeting Working Group, convened in 2011 at the Johns Hopkins Bloomberg School of Public Health, highlighted additional areas in need of further methodological research.<sup>307</sup> Of particular importance, the Working Group Members questioned the validity of network meta-analysis findings in cases where the strength of evidence and risk of bias for different comparisons in the network varied.

Taken in aggregate, previous criticisms of indirect comparisons highlighted the need to demystify the basic assumptions underlying network meta-analysis methods. As Jansen

and Naci stated: “[assumptions] concerning network meta-analysis for both direct and indirect comparisons might be perceived to be more complex, and might be prone to misinterpretation.”<sup>308</sup> To address this important gap in the literature, a number of ‘primer’ articles have recently appeared in high-impact medical journals (including the British Medical Journal [BMJ]),<sup>309</sup> Journal of the American Medical Association [JAMA],<sup>310</sup> and Annals of Internal Medicine<sup>311</sup>), clarifying the assumptions of network meta-analysis, and providing guidance for their conduct and reporting. By focusing on the role of relative treatment effect modifiers (discussed in more detail below), Jansen and Naci also provided a basic explanation for instances where network meta-analysis can be expected to be as valid as pair-wise meta-analysis.<sup>308</sup>

In light of these developments, network meta-analyses are increasingly used in the comparative assessment of new and existing health technologies.<sup>312,313</sup> In fact, over the past decade, there has been an exponential increase in the number of published network meta-analyses.<sup>250</sup> In a widely-cited example, Cipriani and colleagues used this method to compare existing options for the treatment of acute mania.<sup>88</sup> After identifying all published and unpublished trials that compared antimanic drugs either against placebo or against one another, results from 68 studies with more than 16,000 participants were synthesized, allowing for comparative estimates on 13 treatments. This analysis indicated that, based on evidence available to date, antipsychotic drugs (risperidone, olanzapine, and haloperidol in particular) appear to be more effective than mood stabilizers for the treatment of acute mania, emphasizing the need for future treatments to show either greater efficacy or safety than the existing best treatments.

Network meta-analytic approaches are also gaining traction in the United States, with governmental agencies showing interest in the use, reporting, and interpretation of these methods.<sup>314</sup> In a recent example, the United States Agency for Healthcare Research and Quality (AHRQ) commissioned a study to compare the benefits and harms of second-generation antidepressants for treating major depressive disorder in adults. Investigators of the study concluded that, on the basis of a network meta-analysis of 234 studies, no clinically relevant differences in efficacy or effectiveness were detected for the treatment of acute, continuation, and maintenance phases of major depressive disorder.<sup>315</sup>

### 3.3.2.2 *Approach to Network Meta-analysis*

In the network meta-analyses conducted to determine the comparative benefits and harms of individual statins, study-level relative treatment effects were combined using both fixed- and random-effects models within a Bayesian framework employing Markov Chain Monte

Carlo methods.<sup>284</sup> This was based on modeling the outcomes in every treatment group of every study, and specifying the relations among the relative effects across studies making different comparisons.<sup>97,316</sup> For all network meta-analyses, a Bayesian framework was adopted for two reasons. First, network meta-analytic methods are considerably more advanced within the Bayesian framework as compared to frequentist approaches.<sup>279</sup> Second, the results obtained from Bayesian analyses can be interpreted in terms of probabilities, which allow for a more intuitive interpretation of the findings (e.g., “There is an x% probability that drug A is better than drug B”) as opposed to findings obtained from frequentist analyses (which estimate uncertainty in terms of confidence intervals, which are not probability statements).<sup>317</sup> From a Bayesian perspective, every analysis has three elements: the data, which forms the likelihood; the unknown basic parameters which are given a prior distribution and are updated by the information in the likelihood; and a model that expresses the relationship between the basic parameters and the data.<sup>318,319</sup> For the empirical work presented in this thesis, non-informative (vague) priors were used for the unknown basic parameters. Previous research has shown that Bayesian meta-analyses using non-informative priors obtain identical posterior estimates as those obtained from meta-analyses conducted within a frequentist framework.<sup>95</sup>

The network meta-analysis model developed by Dias and colleagues for the National Institute of Health and Care Excellence Decision Support Unit in the United Kingdom was used for all analyses.<sup>320,321</sup> This WinBugs model was generic in the sense that it allowed for any evidence structure (indirect treatment comparison or mixed treatment comparison) and it accounted for the correlation induced on the random treatment effects in multi-arm trials. The model specifications are described in Box 3.4. Examples of WinBugs code for the network meta-analysis models are included in Appendix 2.

**Box 3.4: Analytical Approach to Network Meta-analysis<sup>321,322</sup>**

In the absence of direct head-to-head trial evidence on difference between treatments 2 and 3,  $d_{23}$ , mean  $d_{23}$  and variance  $\sigma^2_{23}$  can be estimated from studies of treatments 1 and 3 with the common comparator 2:

$$d_{23} = d_{13} - d_{12}$$

Where  $d_{13}$  = difference between treatments 1 and 3; and

$$d_{12} = \text{difference between treatments 1 and 2}$$

which can be termed the transitivity assumption of indirect comparisons,<sup>97</sup> and

$$\sigma^2_{23} = \sigma^2_{12} + \sigma^2_{13} - 2\rho^{(1)}_{23}\sigma_{12}\sigma_{13}$$

where  $\rho^{(1)}_{23}$  is the correlation between the relative effects of treatment 3 vs. 1, and the relative effect of treatment 2 vs. 1, within a trial.

The transitivity assumption can be extended to multiple treatments as below:

$$d_{23} = d_{13} - d_{12}$$

$$d_{24} = d_{14} - d_{12}$$

.

$$d_{(s-1),s} = d_{1s} - d_{(1,(s-1))}$$

In this scenario, there are  $(s-1)$  basic parameters to be estimated from the data  $(d_{12}, d_{13}, d_{14}, \dots, d_{1s})$ . The remaining are functional parameters which are functions of the basic parameters.

In this framework of multiple treatment comparisons, the model is specified as below<sup>321,323</sup>:

$$\delta_{i,1k} \sim N(d_{ti1,tik}, \sigma^2)$$

$$r_{jk} \sim \text{Binomial}(p_{jk}, n_{jk}) \text{ for trial } j, \text{ treatment } k$$

$$\text{logit}(p_{jk}) = \begin{cases} \mu_{jb} & b = A, B, C, \dots \text{ if } k = b \\ \mu_{jb} + \delta_{jbk} & \text{ if } k \text{ alphabetically after } b \end{cases}$$

$$\delta_{jbk} \sim \text{Normal}(d_{bk}, \alpha^2) \sim \text{Normal}(d_{Ak} - d_{Ab}, \alpha^2)$$

$$\text{Note: } d_{AA} = 0$$

where  $d_{ti1,tik}$  is the mean treatment effect in arm  $k$  in trial  $i$ ,  $t_{ik}$ , compared to the treatment in arm 1 of trial  $i$ ,  $t_{i1}$ , and  $\sigma^2$  is the between-trial variability in treatment effects. Model specification is identical to traditional pair-wise meta-analysis as shown above, except for the revised notation to account for multiple treatments.

Winbugs, developed by the Medical Research Council Biostatistics Unit at Cambridge University, is the software package that solves these models via Markov Chain Monte Carlo simulation. They output a stream of samples from the posterior distributions,  $P(\theta \mid \text{data})$ , as they are updated with new information from the computed likelihoods,  $P(\text{data} \mid \theta)$ . When the distributions stabilize, sample means of the distributions provide estimates of the basic parameters, e.g.  $d_{12}, d_{13}, d_{14}, \dots, d_{1s}$ .

The results of the network meta-analyses were presented as odds ratios (for binary outcomes) or mean differences (for continuous outcomes) and 95% credible intervals (95%

CrI), which may be interpreted as Bayesian equivalents of 95% confidence intervals. The 95% CrI can be interpreted as indicating a 95% probability that the true mean change falls within the given range. The mean of the posterior distribution and the 95% CrI were plotted in forest-plot graphs to assist in interpretation. The difference between treatments was assessed on the basis of 95% CrIs. Given the Bayesian nature of the statistical analyses, *p* values were not provided for the network meta-analysis results. Instead, statistical significance (although this concept does not apply within a Bayesian framework) was inferred on the basis of 95% CrIs.

In each of the Markov Chain Monte Carlo iterations, each treatment *j* was ranked according to its estimated effect size. Then, the proportion of the iterations in which a given treatment ranked first out of the total gave the probability  $P(j=1)$  that treatment *j* ranked first. Similar probabilities were calculated for being the second best, the third best, and so on:  $P(j=b)$ ,  $b=1,...,a$ . These probabilities added up to one for each treatment and for each rank. To visually demonstrate the statin rankings, rank probabilities  $P(j=b)$  were plotted against the possible ranks  $b = 1,...,a$  for all competing treatments, resulting in 'rankograms'.<sup>324</sup> Rankograms were first developed by Salanti and colleagues in a network meta-analysis of 12 selective serotonin reuptake inhibitors used for the treatment of major depressive disorder.<sup>89</sup> In addition, cumulative probability plots were developed whereby ranks  $b=1,...,a$  were placed on the horizontal axis starting from 1, and the cumulative probability that each treatment was among the top *b* treatments (anywhere between the first and *b*<sup>th</sup> rank) was plotted, following the approach adopted by Salanti and colleagues.

The graphical display of cumulative ranking was supplemented with a numerical summary, which was estimated based on the surface under the cumulative ranking line for each treatment:<sup>324</sup> the surface under the cumulative ranking line was 1 when a treatment was certain to be the best and 0 when a treatment was certain to be the worst. The surface under the cumulative ranking line takes into account not only the magnitude of the effect (OR) but also the uncertainty around it. For each treatment *j* out of the *a* competing treatments, the a vector of cumulative probabilities  $cum_{j,b}$  to be among the *b* best treatments,  $b = 1,...,a$  was calculated. The surface below the cumulative step function for treatment *j* was calculated, as shown by Salanti and colleagues (and implemented in R 2.11.1).

For all binary outcomes of interest, it was assumed that the number of events per trial arm had a binomial distribution. The logit function was used to link the probability of an event in each arm of each trial, the trial-specific baseline effect (treatment effect of the control arm), and the relative treatment effect of the treatment compared with control. Noninformative (i.e., vague or flat) priors  $[N(0, 100^2)]$  were set for trial specific baselines and relative

treatment effects. In the random effects models, noninformative priors were set for the between-trial variance [ $\sigma \sim \text{Uniform}(0,5)$ ].

For all continuous outcomes of interest, it was assumed that the mean change from baseline in outcomes per trial arm had a normal distribution. The identity function was used to link the relative effects across trials making different comparisons, while taking into account the correlations between treatment effects within multi-arm trials. The models adopted noninformative prior distributions for treatment effects [Normal (0, 100<sup>2</sup>)] and the between-trial variance [ $\sigma \sim \text{Uniform}(0,100)$ ] in random effects analyses.

All analyses employed a long burn-in period (50,000 iterations) and follow-up period (80,000-100,000 iterations) to allow for convergence. Trace plots for key parameters for each analysis were reviewed (i.e., visually inspected) to assess convergence in terms of stability. A systematic procedure was followed to ensure that the choice of initial values used in WinBugs models did not have a substantial impact on the findings. The convergence of models in WinBugs was evaluated by performing 3-chain analyses with widely dispersed starting values, and evaluating their convergence using the Brooks-Gelman-Rubin (BGR) diagnostic plots.

The sensitivity of the primary analyses to prior distributions was tested by examining whether the effect sizes and credibility intervals changed after using more informative priors for the between-trial variance in random-effects models. Appendix 4 (Sensitivity of Primary Findings to Prior Distributions) includes the side-by-side comparison of separate analyses using less and more informative priors.

The goodness of model fit was evaluated in WinBugs by calculating the difference between the deviance for the fitted model and the deviance for the saturated model (which fits the data perfectly). Residual deviance,  $D_{\text{res}}$ , was estimated as  $-2(\text{loglikelihood}_{\text{model}} - \text{loglikelihood}_{\text{saturated}})$  whereby the posterior mean of the residual deviance would be roughly equal to the number of unconstrained data points. In each model, the total residual deviance was compared with the total number of data points in the dataset with the expectation that each data point would contribute about one point to the posterior mean deviance. In cases where total residual deviance was considerably higher than the number of individual data points (i.e., 5-7 points), the difference was due to the large number of data points with zero cells. As expected, models could not predict a zero cell since probabilities at zero or one were ruled out, which resulted in the total residual deviance estimates to appear large when there were a large number of zero cells. In addition, the Deviance Information Criterion (DIC) was used to compare different models. DIC is the sum of the posterior mean of the residual deviance and effective number of parameters,  $pD$ . As such, DIC is an extension of the Akaike's Information Criterion and penalizes deviance by the effective number of parameters in the

model. Generally, the model with the lowest DIC was preferred (where a difference of three points or more was deemed meaningful).

### 3.3.2.3 *Checking the Assumptions of Network Meta-analysis*

The assumption employed in network meta-analysis was similar to the one that underlies traditional pair-wise meta-analysis. Often termed *similarity*, network meta-analyses assumed that the distribution of relative treatment effect modifiers (e.g., baseline age of patients and baseline LDL cholesterol level) was balanced across different comparisons in the network of statins. In other words, it was assumed that between-study heterogeneity was independent of the comparison being made. The similarity assumption was first visually investigated by plotting the relationship between baseline study-level covariates such as trial publication year and average patient characteristics such as mean age with relative treatment effects. Second, sub-group analyses were performed for binary variables such as study population (e.g. primary and secondary prevention) and dose. Third, the impact of continuous study-level covariates and average patient characteristics on the relative treatment effect was statistically evaluated using meta-regression analyses.

Meta-regression is a statistical technique that attempts to account for the difference between treatment-effects in a collection of trials by explaining the difference in effect sizes between trials by regressing the effect size from each trial onto trial-level covariates or average participant characteristics. The application of meta-regression techniques to network meta-analysis provides a powerful way of accounting for heterogeneity in complex evidence networks. Meta-regressions conducted in the context of network meta-analyses require a careful examination of potential covariates, and the selection of covariates should be based on *a priori* exploratory analyses. Although there are a number of covariates that can be used to explain the heterogeneity between included studies, multiple analyses using a large number of covariates would have a high probability of finding false-positive explanatory variables.<sup>325</sup> In addition, as shown by Jansen and colleagues, adjusting for covariates that are not relative treatment effect modifiers would actually introduce bias into the findings of network meta-analysis.<sup>288</sup>

The meta-regression approach has two potential limitations. First, it is important to note that, while the studies used in the meta-regression are all randomized controlled trials, the relationship identified by the meta-regression is an observational relationship between the treatment effect and study-level covariates or average patient characteristics (covariates are not randomized across different studies).<sup>326</sup> The second is autocorrelation where the sampled estimates of parameters in the model may be highly correlated.

Recognizing these limitations, meta-regression analyses were used judiciously and the qualitative approach of visually inspecting clinically meaningful heterogeneity was prioritized over the statistical alternative. The study-level covariates of interest were selected following a review of the literature. Given the wealth of previous meta-analyses conducted on statin trials, there was ample information on which factors would potentially modify the relative treatment effects of statins. These included factors evaluated in previous meta-analyses such as baseline mean age and baseline mean LDL cholesterol level. In addition, trial publication year was included to examine whether the comparative effects of individual statins would be different over time (essentially using trial publication year as a proxy for a host of factors such as advances in trial design over time, changes in clinical practice, etc.). For clinical outcomes, the potential association between baseline risk and treatment effect was also investigated as a possible explanation of between-study heterogeneity. Although gender was originally specified as a potential relative treatment effect modifier, recent meta-analyses have demonstrated that the comparative effects of statins are not influenced by gender.<sup>242</sup> Accordingly, gender was not evaluated further. As described in Chapter 7 entitled '*Methodological Quality and Risk of Bias in the Randomized Trials of Statins*' potential industry sponsorship bias was also evaluated using a meta-regression approach.

Meta-regression analyses were performed by allowing for a common treatment-covariate interaction for each statin compared to control.<sup>327</sup> This approach was taken under the assumption that there was no interaction between treatment and study-level covariates or average patient characteristics. A random-effects model was employed to allow for heterogeneity not explained by the covariates. The random-effects meta-regression model, developed by Cooper and colleagues (and implemented in WinBugs),<sup>327</sup> was specified as below (as described in Chapter 7, a fixed-effect specification was also tested for the industry sponsorship bias analysis):

$$r_{jk} \sim \text{Binomial}(p_{jk}, n_{jk}) \text{ for trial } j, \text{ treatment } k$$

$$\text{logit}(p_{jk}) = \begin{cases} \mu_{jb} & b = A, B, C, \dots \text{ if } k = b \\ \mu_{jb} + \delta_{jkb} & \text{if } k \text{ alphabetically after } b \end{cases}$$

$$\delta_{jkb} \sim \begin{cases} \text{Normal}(d_{Ak} + \beta X_j, \sigma^2) \sim \text{Normal}(d_{Ak} - d_{AA} + \beta X_j, \sigma^2) & \text{if } b = A \\ \text{Normal}(d_{bk}, \sigma^2) \sim \text{Normal}(d_{Ak} - d_{Ab}, \sigma^2) & \text{if } b \neq A \end{cases}$$

Note:  $d_{AA} = 0$

A separate meta-regression analysis was conducted for each of the three potential relative treatment effect modifiers to evaluate whether each study-level covariate had an effect on the observed relative treatment effects. Multiple study-level covariates were not considered

in the same meta-regression model given the insufficient power to estimate more complex models.<sup>328</sup>

Findings of different meta-regression models were first compared qualitatively to examine any clinically meaningful differences across point estimates and 95% CrI in different sets of analyses. In addition, the estimate of the between-study heterogeneity was compared to see if adding covariates in meta-regression analyses could explain the between-study heterogeneity.

#### 3.3.2.4 Evaluation of Consistency in the Network Meta-analysis

A further assumption of *consistency* was made in combining direct and indirect evidence. This assumption implied that, even when the indirect comparison was valid, it was possible for the indirect evidence to be inconsistent with evidence obtained from head-to-head trials because of clinically meaningful imbalances in the distribution of relative treatment effect modifiers across different treatment comparisons. Inconsistency was then defined as the discrepancy between different types of comparisons when direct and indirect sources of evidence were combined in a network meta-analysis.

It is important to note that both *similarity* and *consistency* considerations rest on the assumption that there is no association between the distribution of effect modifiers across studies and the type of treatment comparisons.<sup>308</sup> The presence of an association between the distribution of effect modifiers across studies and the type of treatment comparisons would result in biased relative estimates in any meta-analysis that employs an indirect comparison – regardless of the structure of the evidence network.<sup>308</sup>

To check for inconsistency, two alternative methods were adopted. For the analyses comparing the clinical benefits and harms of individual statins, the so-called “Bucher method” was adopted.<sup>329</sup> Song and colleagues previously used this method in their assessment of the validity of indirect comparisons.<sup>289,290</sup> This was based on conducting a random-effects traditional meta-analysis on all comparisons using the DerSimonian-Laird method, and calculating the difference in log odds ratios between direct and indirect estimates for each closed loop of the network (i.e., in instances when both direct and indirect comparisons could be generated for each contrast in the network). As Bucher and colleagues specified, in a closed loop of treatments A, B, and C, the indirect comparison between treatments A and B can be obtained from the direct comparison between treatments A and C, and the direct comparison between treatments B and C:

$$\log(OR_{AB}) = \log(OR_{AC}) - \log(OR_{BC})$$

The variance of this indirect estimate is then given by:

$$\text{variance}(\log OR_{AB}) = \text{variance}(\log OR_{AC}) + \text{variance}(\log OR_{BC})$$

The inconsistency in this closed loop comparing treatments A, B, and C can be estimated as:

$$\Delta_{ABC} = \ln OR_{ACdirect} - \ln OR_{ACindirect}$$

$$\text{variance}(\Delta_{ABC}) = \text{variance}(\ln OR_{ACdirect}) + \text{variance}(\ln OR_{ACindirect})$$

The statistical significance of inconsistency is then tested by:

$$Z = \frac{\Delta_{ABC}}{\sqrt{\text{variance}(\Delta_{ABC})}} \sim N(0,1)$$

The assessment of consistency was repeated for each closed loop in the treatment network, using the automated functions developed by Salanti and colleagues. The inconsistency for each closed loop was visualized in forest plots (termed inconsistency plots) to inspect potential discrepancies between direct and indirect evidence in the treatment network. Graphical presentation of inconsistency plots was developed in R 2.11.1.

Given the extremely large numbers of pair-wise meta-analyses required to use the Bucher method, an alternative method was employed to check for the consistency assumption in the analyses that evaluated the dose-comparative effects of individual statins (all six statins at low, medium, and high doses). The consistency of relative treatment effects obtained from an analysis of head-to-head trials (i.e. direct evidence) with those obtained from an analysis combining both placebo-controlled and active-comparator trials (i.e. mixed evidence) were plotted and qualitatively compared for instances where the 95% CrIs did not overlap. Potential discrepancy was assessed in terms of the direction of effect, as well as its magnitude.

### 3.4 Deviations from the Protocol

There were a number of deviations from the original protocol. These can be categorized as changes in the approach to (1) study identification and data extraction; (2) dose evaluation; (3) consistency exploration; (4) sensitivity analysis; and (5) outcomes of interest.

*Study identification and data extraction:* In terms of the electronic database searches, Database of Abstracts of Reviews of Effects, National Health Service Economic Evaluation Database, and Health Technology Assessment Database were not searched. In addition, the trial databases of regulatory agencies (the Food and Drug Administration in the United States, the Medicines and Healthcare products Regulatory Agency in the United Kingdom and the European Medicines Agency in the European Union) and ongoing trial registers (clinicaltrials.gov in the United States and National Research Register in the United Kingdom) were not hand-searched for unpublished and ongoing randomized controlled

trials. This change was justified for two reasons. First, many of the statin trials were conducted before mandatory trial registers such as [clinicaltrials.gov](http://clinicaltrials.gov) were established<sup>330</sup> (the International Committee of Medical Journal Editors policy requiring the registration of clinical trials as a prerequisite for consideration for publication was only implemented in 2005).<sup>331</sup> Second, searching MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials was considered to be adequate to identify the published randomized controlled trials of statins. As outlined in the previous Chapter (*Chapter 2: Evolution of Clinical Evidence: The Case of Statins*), a large number of systematic reviews and meta-analyses have evaluated the benefits and harms of statins. To ensure that the search strategy was robust and that all relevant trials were identified, the reference lists of *all* previous meta-analyses were documented and manually reviewed. Although the protocol suggested that two researchers would extract data independently, one researcher was responsible for all aspects of data extraction. However, two additional researchers assisted in checking the accuracy of data extraction.<sup>9</sup>

*Dose evaluation:* The impact of dose on the comparative benefits and harms of individual statins was evaluated using a different approach than what was originally proposed in the protocol. The protocol specified that a meta-regression technique would be used to take into account the dose-response relationship for each individual statin. Upon further consideration, this was deemed to be potentially inappropriate for a meta-analysis aimed at determining relative treatment effects of multiple treatments. The primary concern was that randomization would not be maintained when arm-level factors (i.e., dose differences between different arms within a trial) were taken into account. Accordingly, the impact of dose was evaluated in sub-group analyses whereby all statin-dose combinations were treated as independent treatments in the network. Although novel statistical approaches can take into account dose-effects as sub-nodes in a network of randomized controlled trials,<sup>332</sup> a qualitative approach was preferred over its statistical alternative. Whether or not to group individual statins at different doses as a single node in the network was further informed by discussions with clinician collaborators. In the end, each statin-dose combination was treated as a different treatment and no trends or statistical relationships were fitted or assumed.

*Consistency evaluation:* As described in the previous section, the consistency assumption was evaluated using the “Bucher method.”<sup>329</sup> Unlike what was originally proposed in the protocol, a node-splitting approach was not used. The primary difference between these approaches is that the Bucher method compares direct and indirect evidence within each

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<sup>9</sup> Given that this systematic review of the literature was undertaken specifically for this dissertation, as the principle researcher, I was responsible for all aspects of the systematic review including data extraction.

closed loop whereas the node-splitting approach compares direct evidence with indirect evidence obtained from the entire network. In the absence of statistically detectable inconsistency within each loop for the clinical benefit and harm outcomes (as discussed in more detail in Chapter 5: *Comparative Benefits of Individual Statins* and Chapter 6: *Comparative Harms of Individual Statins*), the node-splitting approach was not used. Instead, meta-regression analyses were conducted to evaluate the potential impact of known relative treatment modifiers in the network meta-analysis.

*Sensitivity analysis:* The effect of trial duration on the comparative effects of individual trials was evaluated but not reported. This decision was made following an exploratory analysis demonstrating that trial duration did not have an effect on the reported cholesterol-lowering effects of individual statins. For clinical and harm outcomes, follow-up durations (and times at which trial results were reported) were surprisingly consistent across groups of trials reporting different types of outcomes. For instance, clinical endpoints (such as mortality and major coronary events) were almost always reported in trials with follow-up durations longer than 52 weeks. Similarly, trials reporting cancer or diabetes occurrence had longer follow-up durations.

*Outcomes of interest:* In addition to the surrogate and clinical outcomes listed in the original protocol, network meta-analyses were conducted on harm and tolerability outcomes. The decision to expand the scope of the network meta-analyses by including additional outcomes was based on the clinical relevance of these additional endpoints for prescribers. Prescribers are often faced with a decision to choose among seemingly similar statins on the basis of not only benefit outcomes but also harm and tolerability outcomes. Accordingly, the following endpoints were added *post hoc* to the list of outcomes: discontinuations due to adverse events, occurrence of myalgia, hepatic transaminase elevations, creatine kinase elevations, diabetes, cancer, and rhabdomyolysis. This comprehensive list of endpoints was selected on the basis of outcomes considered in previous meta-analyses. An additional outcome that could potentially be included – but was not due to data limitations in randomized controlled trials – was acute kidney injury.

## Chapter 4

### Dose-Comparative Effects of Individual Statins on Cholesterol Concentrations\*

Clinical practice guidelines identify LDL cholesterol as the primary target of cholesterol lowering therapy for the primary and secondary prevention of cardiovascular disease.<sup>154</sup> The National Cholesterol Education Program's Third Adult Treatment Panel (ATP-III) and ACC/AHA clinical practice guidelines recommend that statins should be considered as first-line treatment when cholesterol-lowering drugs are indicated to lower the risk of cardiovascular events. In addition to their effect on LDL and Total cholesterol concentrations, statins result in modest increases in HDL cholesterol, which is a negative risk factor for cardiovascular disease (i.e., presence of high HDL cholesterol removes one risk factor from the total count of risk factors). Because of their efficacy in reducing LDL cholesterol and increasing HDL cholesterol and their favorable tolerability and safety profile, statins are the most commonly prescribed agents for the primary and secondary prevention of cardiovascular disease.

At the time of developing the protocol for this research, there were six statins available on the market (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin), which were originally indicated as monotherapy for the reduction of elevated LDL cholesterol concentrations (Table 4.1). Pitavastatin (Livalo®) was approved and marketed in the United States in June 2010 following its evaluation by the Food and Drug Administration in August 2009. Pitavastatin is not included in the dose-comparative analyses presented in this chapter. There are important differences among the currently marketed statins in terms of their chemical, pharmacodynamic, and pharmacokinetic properties.<sup>333</sup> Lovastatin, pravastatin, and simvastatin are derived from fungal fermentation whereas fluvastatin, atorvastatin, and rosuvastatin are entirely synthetic. Individual statins

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\* Part of the work presented in this chapter was published with the following reference: Naci H, Brugts JJ, Fleurence R, Ades AE. Dose-comparative effects of individual statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. *Eur J Prev Cardiol.* 2013 Aug;20(4): 658-70.

differ in the degree of LDL cholesterol lowering that can be achieved per mg dose, and the differences in comparative effects on cholesterol concentrations are attributed to their pharmacodynamic and pharmacokinetic differences.

**Table 4.1** – Summary of currently marketed statins (excluding combination therapies and pitavastatin).

Available statins	Usual starting dose	Maximum FDA-approved dose	Available preparations
Atorvastatin * (Lipitor®)	10 mg	80 mg	10, 20, 40, 80 mg tablets
Fluvastatin * (Lescol®)	20 mg	80 mg	20, 40 mg capsules, 80 mg extended release tablets
Lovastatin * (Mevacor®)	20 mg	80 mg	10, 20, 40 mg tablets
Pravastatin * (Pravachol®)	20 mg	80 mg	10, 20, 40 mg tablets
Rosuvastatin (Crestor®)	10 mg	40 mg	5, 10, 20, 40 mg tablets
Simvastatin * (Zocor®)	20 mg	80 mg	5, 10, 20, 40, 80 mg tablets

*\* Also available as a generic.*

Dose-comparative effects of individual statins on cholesterol concentrations have been previously studied. In 1997, Kong and colleagues performed a meta-analysis to quantify the comparative effects of individual statins on LDL, HDL, and Total cholesterol concentrations.<sup>334</sup> Based on 52 double-blind, fixed-dose, placebo-controlled trials of fluvastatin, lovastatin, pravastatin, and simvastatin, reductions in baseline LDL cholesterol concentrations ranged from 19% with pravastatin 10 mg/day to 41% with simvastatin 40 mg/day. The comparative effects of individual statins were also explored by Law and colleagues in a meta-analysis that aimed to determine the extent to which statins reduce serum concentrations of LDL cholesterol according to dose.<sup>148</sup> Their meta-analysis of 164 short-term (which typically lasted a few weeks), double-blind, fixed-dose, placebo-controlled trials of six statins included approximately 24,000 individuals. According to this analysis, there was a clear dose-response relationship with higher doses resulting in greater reductions in LDL cholesterol concentrations. The estimated reductions in LDL cholesterol were 55% with atorvastatin 80 mg/day, 40% with atorvastatin 10 mg/day, lovastatin 40 mg/day, simvastatin 40 mg/day, or rosuvastatin 5mg/day, whereas pravastatin and fluvastatin achieved smaller reductions.

Edwards and colleagues performed a meta-analysis of randomized, double-blind, placebo-controlled trials assessing the effect of seven statins (including cerivastatin, which was

subsequently withdrawn from the market) on cholesterol concentrations in patients with high blood cholesterol.<sup>335</sup> Trials were eligible for inclusion in this meta-analysis if they lasted longer than 12 weeks and included at least 20 patients per treatment group. Based on a total number of 68,000 individuals, reductions in Total cholesterol of 25% or more and LDL cholesterol of more than 30% were recorded for fixed doses of simvastatin 40 mg/day, atorvastatin 10 mg/day, and rosuvastatin 5 mg/day and rosuvastatin 10 mg/day. This meta-analysis concluded that the duration of the trial and baseline cholesterol concentrations did not have an impact on the results.

An important limitation of these earlier meta-analyses is that they relied solely on placebo-controlled trials, without taking into account direct head-to-head trials. In addition, placebo-controlled trials for each statin-dose combination were pooled separately. In other words, separate meta-analyses were performed for atorvastatin at low, medium, and high doses, simvastatin at low, medium, and high doses, and so on. This resulted in an enormous loss of valuable data given that a large number of direct head-to-head trials evaluated the dose-comparative effects of statins. For example, CURVES (comparative dose efficacy study of atorvastatin versus statins) was a multicenter, randomized, open-label, parallel-group, 8-week study including 534 patients, which evaluated the comparative dose efficacy of atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin at various dosing regimens.<sup>336</sup> Similarly, STELLAR (Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin) was a 6-week, parallel-group, open-label, randomized, multicenter trial including 2,431 individuals, which compared atorvastatin, pravastatin, rosuvastatin and simvastatin across dose ranges for reduction of LDL cholesterol.<sup>337</sup> These trials, and many others that directly compared individual statins head-to-head, provide valuable information about the dose-comparative effects of statins and should be incorporated into meta-analyses.

Given the large body of literature evaluating the cholesterol reducing effects of individual statins at different doses, later reviews and meta-analyses investigated the dose-comparative effects of statins on cholesterol concentrations. However, these studies focused on two statins at a time – without a clear indication of the dose-comparative effects of all statins simultaneously. One example was the meta-analysis by Rogers and colleagues, which compared the effects of atorvastatin and simvastatin in 18 direct head-to-head randomized trials at doses ranging from 10 to 80 mg/day.<sup>338</sup> Another example was the analysis performed by Wlodarczyk and colleagues, which compared atorvastatin and rosuvastatin across various dosing strategies.<sup>339</sup> This meta-analysis included 25 open-label and double-blind randomized trials including approximately 20,000 individuals.

In an attempt to simultaneously compare the dose-comparative effects of multiple statins on the basis of direct head-to-head trials, the systematic review conducted by the Drug Effectiveness Review Project (and previously the Veterans Health Administration Pharmacy Benefits Managements Strategic Healthcare Group) included 102 head-to-head comparisons of different statins to address the question: “How do statins ... compare in their ability to reduce [LDL and HDL] cholesterol?”<sup>340</sup> Although this review did not perform a formal statistical analysis to estimate the pooled effects of each statin-dose combination and the statistical uncertainty around these estimates, it qualitatively estimated the approximate equivalent daily doses for statins with respect to their LDL cholesterol lowering abilities, presented in a ‘dose-equivalence chart’ (Table 4.2). A similar qualitative approach was later adopted by Weng and colleagues in a systematic review on the therapeutic equivalence of statins.<sup>341</sup> This dose-equivalence chart of statins has since been widely cited in publicly available reference materials.

**Table 4.2** – Equivalent daily doses of statins as reported by the Drug Effectiveness Review Project.

Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
--	40 mg	20 mg	20 mg	--	10 mg
10 mg	80 mg	40 or 80 mg	40 mg	--	20 mg
20 mg	--	80 mg	80 mg	5 or 10 mg	40 mg
40 mg	--	--	--	--	80 mg
80 mg	--	--	--	20 mg	--
--	--	--	--	40 mg	--

The analytic approach for obtaining this oft-cited dose-equivalence chart of statins has significant drawbacks. First, it does not take into account the correlations in relative treatment effect estimates that arise from trials with more than two treatment arms (multi-arm trials). Second, comparisons are implicitly indirect, neither taking into account potential differences between baseline characteristics nor maintaining randomization within trials. Qualitatively – and informally – comparing findings from separate pooled analyses does not take into account the uncertainty around their point estimates. It is essential to provide an effect estimate for the difference between treatments as well as a measure of the level of uncertainty around that estimate. As a result of these limitations, statin-dose combinations that appear different on the basis of point estimates may in fact be statistically equivalent when taking into account the uncertainty around the point estimate. A network meta-analysis approach that simultaneously combines direct and indirect

sources of evidence in a single analysis that maintains study-level randomization and accommodates the correlation structure in multi-arm trials would address these limitations.

To date, there has been no comprehensive analysis of the dose-comparative effects of statins on cholesterol levels that builds on the totality of the randomized trial evidence. This has important implications for clinical practice as prescribers do not have adequate evidence on the comparative effects of different statins on serum cholesterol levels based on direct and indirect meta-analyses. The objective of the empirical analysis presented in this chapter was to perform an all-encompassing review of the statin randomized trial literature and quantify the dose-comparative effects of individual statins on serum cholesterol levels by combining both placebo-controlled and active-comparator trials. This chapter reports the findings of the network meta-analysis on the effect of different statins on serum LDL cholesterol, total cholesterol, and HDL cholesterol.

#### **4.1 Empirical Considerations**

As outlined in Chapter 3 (*Evidence Review and Synthesis Methods*), separate network meta-analyses were performed for the mean change from baseline in serum LDL cholesterol, HDL cholesterol, and Total cholesterol between two comparator treatments for a given dose (change from baseline in the treatment group minus that in the control group). The primary outcome of interest was LDL cholesterol reduction from pretreatment levels. To obtain a comprehensive estimate of the comparative effect of statins at different doses on serum lipid levels, the base-case network meta-analysis pooled all primary and secondary prevention trials in addition to trials with mixed patient populations, including all placebo-controlled and active-comparator trials eligible for inclusion in the systematic review. In addition, for the primary outcome of LDL cholesterol reduction from pretreatment levels, separate analyses for the primary and secondary prevention populations were conducted to evaluate whether the dose-comparative effects of statins differed between individuals with and without coronary heart disease at baseline.

*Consideration of dose in the network meta-analysis:* The base-case statistical analysis was inclusive of fixed-dose and titration designs. Accordingly, trials that allowed variable dosing regimens (titrating) were included. Whenever possible, data from the fixed dosing period were used for titration designs. If all patients were force-titrated to a given dosage, data from the final high-dose period were used. Where trials provided data on the proportion of patients at different doses, the number in the treatment arm was proportioned out to different dosages.

All analyses were dose-specific and explored the effects of individual statins at different doses separately. Each possible statin-dose combination was considered as a different

treatment and no trends were fitted or assumed. The following daily doses were considered for atorvastatin, lovastatin, pravastatin, and simvastatin:  $\leq 10$  mg (10),  $>10$  and  $\leq 20$  mg (20),  $>20$  and  $\leq 40$  mg (40), and  $>40$  mg (80). For fluvastatin, daily doses were  $\leq 20$  mg (20),  $>20$  and  $\leq 40$  mg (40), and  $>40$  mg (80). For rosuvastatin, the daily doses were  $\leq 5$  mg (5),  $>5$  and  $\leq 10$  mg (10),  $>10$  and  $\leq 20$  mg (20), and  $>20$  mg (40). All analyses were based on the total number of randomly assigned participants if the study authors did not perform intention-to-treat analyses.

*Ranking of statins in the network meta-analysis:* The probability that each statin-dose combination is the best regimen was estimated by calculating its treatment effect compared with common comparator treatment, and counting the proportion of iterations of the Markov chain in which each statin-dose combination has the highest treatment effect, the second highest, and so on. Rank probabilities were separately estimated for LDL cholesterol and Total cholesterol. Rankograms were developed to graphically present the distribution of ranking probabilities. In addition, cumulative probability plots were developed for each outcome and the surface area under the cumulative ranking line for each statin-dose combination was estimated as described in Chapter 3 (*Evidence Review and Synthesis Methods*). The surface area under the cumulative ranking line provided a numerical summary of the overall score for each statin-dose combination for each outcome. Each statin was scored with points up to a maximum of 1.00, which was the weighted sum of scores separately estimated for LDL cholesterol and Total cholesterol.

*Assessment of heterogeneity and inconsistency in the network meta-analysis:* Whether the potential heterogeneity and inconsistency across the evidence base in the network meta-analysis for the primary outcome of LDL cholesterol lowering could be explained by baseline mean age, baseline mean LDL cholesterol concentration, or publication year was investigated using meta-regression analyses. All meta-regression analyses were performed by allowing for a common treatment-covariate interaction for each statin compared to control, as described in Chapter 3 (*Evidence Review and Synthesis Methods*). A separate meta-regression analysis was conducted for each of the three potential relative treatment effect modifiers to evaluate whether each study-level covariate had an effect on the observed relative treatment effects. Multiple study-level covariates were not considered in the same meta-regression model given the insufficient power to estimate more complex models.<sup>328</sup>

To further explore any potential inconsistency between direct and indirect evidence, the consistency of relative treatment effects obtained from an analysis of head-to-head trials (i.e. direct evidence) with those obtained from an analysis combining both placebo-controlled and active-comparator trials (i.e. mixed evidence) were qualitatively evaluated.

The consistency of the relative treatment effects for potential differences between estimates obtained from two sets of analyses (i.e. direct and mixed estimates) were plotted and visually inspected. This approach was preferred over the Bucher method given the large number of pair-wise meta-analyses that needed to be conducted and compared for 23 statin-dose combinations, which would result in 276 pair-wise meta-analyses.

*Presentation of results:* First, the findings of the network meta-analysis, which combined evidence from placebo-controlled and active-comparator trials, were presented. This was followed by the presentation of meta-regression results, which provided a statistical assessment of heterogeneity and inconsistency in the network meta-analysis on the basis of study-level covariates (i.e. baseline mean age, baseline mean LDL cholesterol levels, and publication year).

*Interpretation of results:* Given the Bayesian nature of network meta-analyses, the findings of these analyses were presented as mean changes from baseline and 95% CrIs. If a 95% CrI did not include the null value 0.00, this was interpreted as indicating <5% probability that there was no difference between the two comparators. The findings were considered 'statistically significant' when the 95% CrI did not include the null value 0.00.

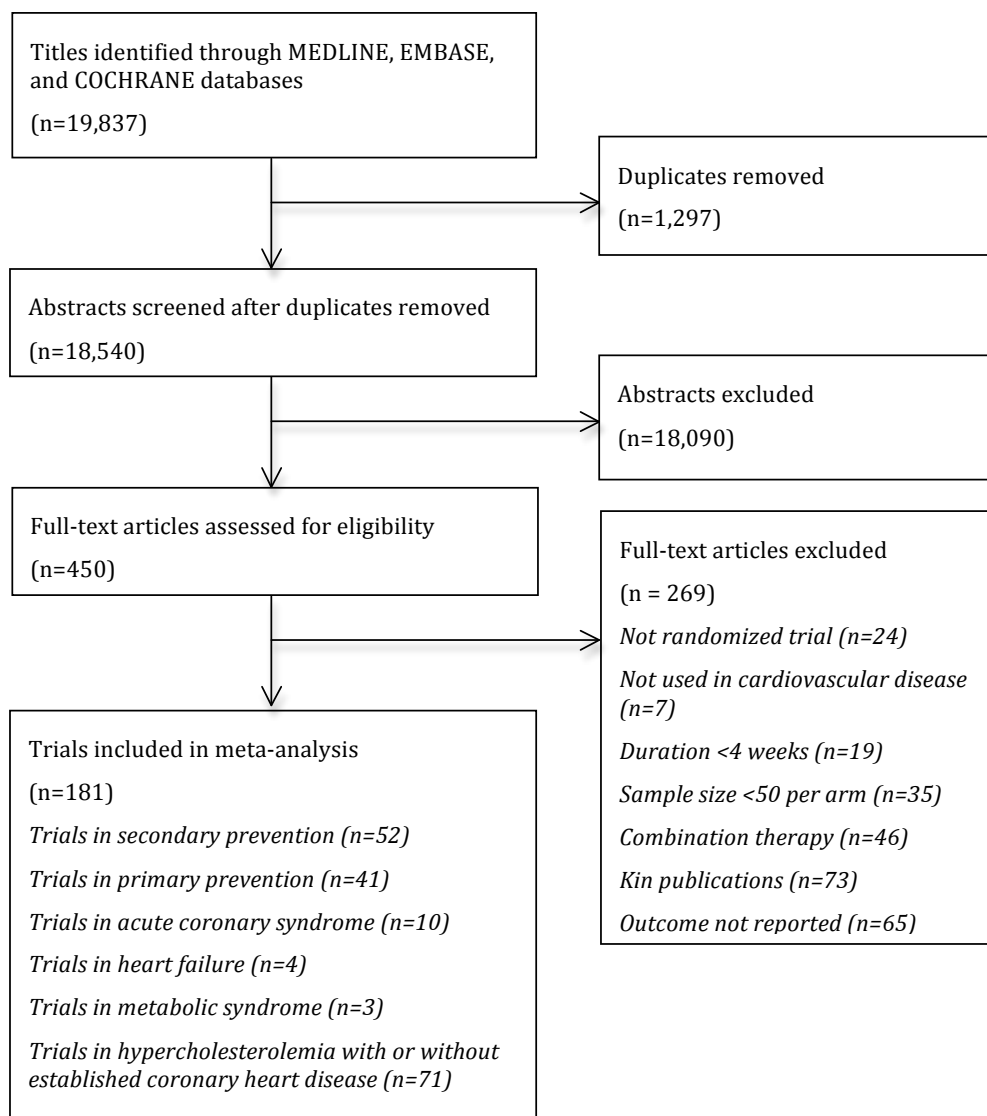
## **4.2 Systematic Review Findings**

There were 181 randomized controlled trials included in the systematic review and network meta-analysis of serum lipid outcomes (Figure 4.1). These trials included a total of 256,827 individuals. 112 trials were double-blind while 55 were open-label and two were single-blind. Blinding was not clear for the remaining 12 trials. Overall, the average trial duration was 66 weeks, with 53 trials reporting serum lipid levels after at least one year of follow up. There were 52 trials conducted among individuals with established coronary heart disease; 41 trials were in primary prevention (eight of which were among individuals with diabetes); 10 included patients with acute coronary syndromes; four included patients with heart failure; and three were among patients with metabolic syndrome. The remaining 71 trials included individuals with hypercholesterolemia with or without established coronary heart disease.

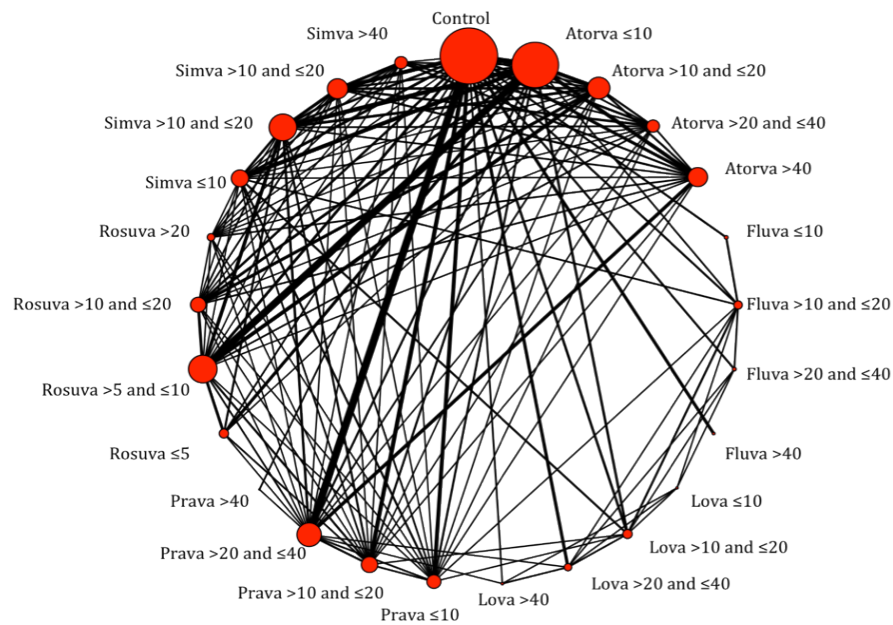
Figure 4.2 shows the network of eligible pair-wise comparisons for LDL, Total, and HDL cholesterol reductions from baseline in placebo-controlled and active-comparator trials of individuals across all populations. Of the 15 possible pair-wise comparisons between the six statins, 11 were available in the identified literature. No trial directly compared all statin-dose combinations to each other. There were 83 two-armed placebo-controlled trials and the remaining 98 were two- or multi-armed active-comparator trials. Of these 98 active-comparator trials, 60 were two-arm active-comparator trials, 21 were multi-arm active-

comparator trials, and 17 were multi-arm trials including a placebo comparison. The frequency of direct head-to-head comparisons varied widely by statin type. For instance, most frequent comparisons occurred between rosuvastatin and atorvastatin (N=30). There were only a few trials that evaluated fluvastatin, particularly at its lowest dosages (N=14).

**Figure 4.1** – Flow diagram of trial identification and selection.



**Figure 4.2** – Network of available comparisons for determining dose-comparative effects of individual statins on cholesterol levels.\*

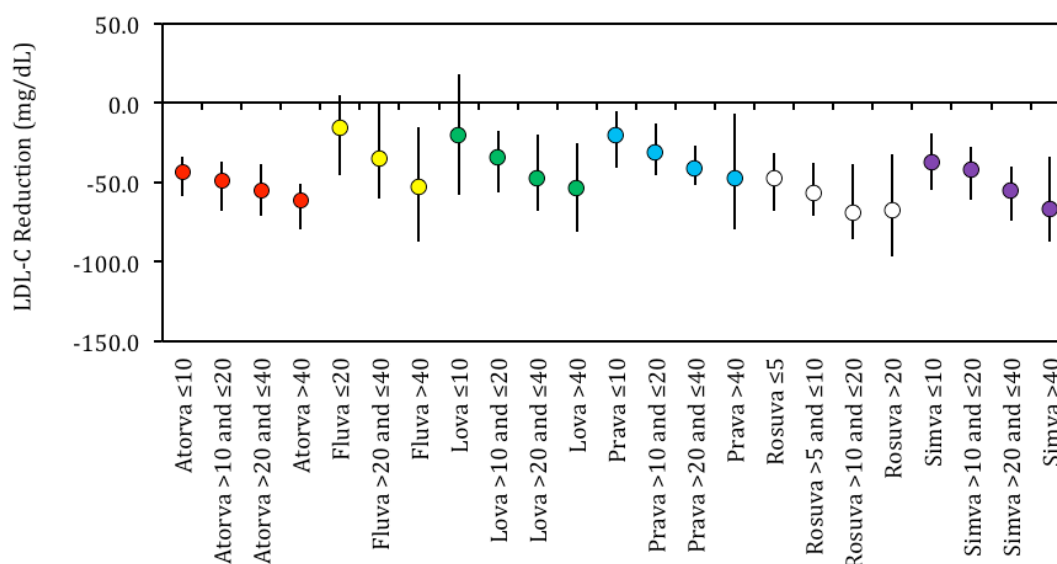


\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants. Atorva: atorvastatin, fluva: fluvastatin, lova: lovastatin, prava: pravastatin, rosuva: rosuvastatin, simva: simvastatin.

### 4.3 Dose-comparative Effects of Statins on Serum Lipid Levels

Differential dose-comparative effects of individual statins on serum LDL cholesterol levels are shown in Figure 4.3 and Table 4.3. Higher statin doses were generally associated with greater relative reductions in pretreatment LDL cholesterol levels as compared to control treatment. According to the network meta-analysis results, atorvastatin, pravastatin, rosuvastatin, and simvastatin were significantly better than control treatment at all dosing regimens in terms of reducing baseline concentrations of LDL cholesterol. However, fluvastatin at  $\leq 20$  mg/day (-15.46 mg/dL, 95% CrI: -45.66 to 4.62 mg/dL), fluvastatin between  $>20$  and  $\leq 40$  mg/day (-34.51 mg/dL, 95% CrI: -60.29 to 0.62 mg/dL) and lovastatin at  $\leq 10$  mg/day (-20.33 mg/dL, 95% CrI: -57.98 to 18.02 mg/dL) did not result in significant reductions from baseline LDL cholesterol levels as compared to control treatment (Table 4.3). Atorvastatin at  $>40$  mg/day (-60.82 mg/dL, 95% CrI: -80.06 to -50.86 mg/dL), rosuvastatin between  $>10$  and  $\leq 20$  mg/day (-69.24 mg/dL, 95% CrI: -85.59 to -38.81 mg/dL), rosuvastatin between  $>20$  and  $\leq 40$  mg/day (-67.54 mg/dL, 95% CrI: -96.74 to -32.46 mg/dL), and simvastatin at  $>40$  mg/day (-66.87 mg/dL, 95% CrI: -87.66 to -33.99 mg/dL) resulted in the greatest reductions in pretreatment LDL cholesterol concentrations as compared to control treatment.

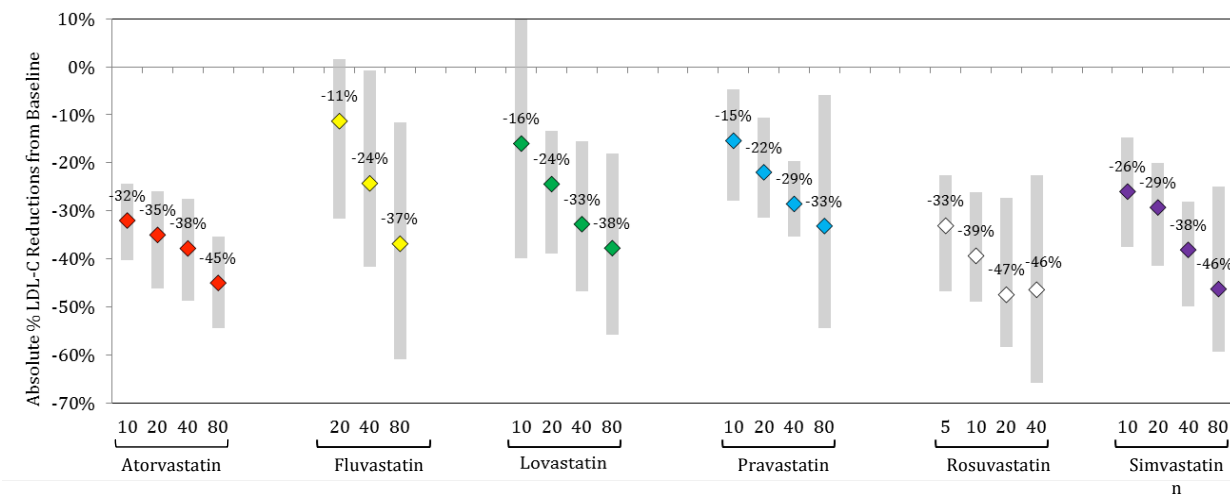
**Figure 4.3** – Dose-comparative relative effects of statins on serum LDL cholesterol levels.\*



\* Estimates shown are mean changes (mean, 95% CrI) from baseline in serum LDL cholesterol concentrations as compared to control treatment. LDL-C: low-density lipoprotein cholesterol, atorva: atorvastatin, fluva: fluvastatin, lova: lovastatin, prava: pravastatin, rosuva: rosuvastatin, simva: simvastatin.

Figure 4.4 shows the estimated percentage reductions from an average baseline concentration of 150 mg/dL (approximate mean of pretreatment LDL cholesterol concentrations in the included trials). Atorvastatin (32% at  $\leq 10$  mg/day to 45% at  $>40$  mg/day), pravastatin (15% at  $\leq 10$  mg/day to 33% at  $>40$  mg/day), rosuvastatin (33% at  $\leq 5$  mg/day to 47% at  $>20$  mg/day), and simvastatin (26% at  $\leq 10$  mg/day to 46% at  $>40$  mg/day) at all dosing regimens significantly reduced LDL cholesterol levels from average baseline levels of approximately 150 mg/dL whereas low dosing regimens of fluvastatin (11% reduction, 95% CrI: 32% reduction to 2% increase at 20 mg/day) and lovastatin (16% reduction, 95% CrI: 40% reduction to 10% increase) did not significantly reduce LDL cholesterol levels.

**Figure 4.4** – Dose-comparative absolute effects of statins on serum LDL cholesterol concentrations.\*



\* Estimates shown are absolute reductions (mean, 95% CrI) at all dose combinations standardized to the average pretreatment LDL cholesterol concentration in the included set of trials. LDL-C: low-density lipoprotein cholesterol.

**Table 4.3 – Dose-comparative relative effects of statins on serum lipid concentrations.\***

**(A)**

	≤5 mg/day	>5 and ≤10 mg/day	>10 and ≤20 mg/day	>20 and ≤40 mg/day	>40 mg/day
<b>Atorvastatin</b>	---	-43.16 (-58.77, -34.08)	-48.33 (-67.89, -36.77)	-54.79 (-70.88, -38.63)	-60.82 (-80.06, -50.86)
<b>Fluvastatin</b>	---	---	-15.46 (-45.66, 4.62)	-34.51 (-60.29, 0.62)	-52.8 (-87.54, -15.10)
<b>Lovastatin</b>	---	-20.33 (-57.98, 18.02)	-34.37 (-56.22, -17.54)	-47.15 (-68.26, -20.21)	-53.41 (-81.61, -25.38)
<b>Pravastatin</b>	---	-20.41 (-40.62, -4.98)	-31.12 (-45.85, -12.91)	-40.77 (-51.68, -27.00)	-47.14 (-79.49, -7.10)
<b>Rosuvastatin</b>	-47.37 (-68.37, -31.64)	-56.85 (-71.45, -37.59)	-69.24 (-85.59, -38.81)	-67.54 (-96.74, -32.46)	---
<b>Simvastatin</b>	---	-36.98 (-54.78, -19.25)	-41.69 (-60.71, -27.42)	-54.92 (-74.13, -39.91)	-66.87 (-87.66, -33.99)

**(B)**

	≤5 mg/day	>5 and ≤10 mg/day	>10 and ≤20 mg/day	>20 and ≤40 mg/day	>40 mg/day
<b>Atorvastatin</b>	---	-49.49 (-63.63, -37.82)	-66.75 (-88.38, -47.49)	-71.55 (-94.70, -41.28)	-79.22 (-101.2, -57.75)
<b>Fluvastatin</b>	---	---	-19.82 (-61.95, 10.99)	-26.27 (-72.20, 20.00)	-28.41 (-80.73, 5.70)
<b>Lovastatin</b>	---	-34.66 (-75.46, 22.64)	-40.21 (-60.72, -16.24)	-24.94 (-60.82, -0.54)	-67.26 (-105.60, -30.90)
<b>Pravastatin</b>	---	-30.07 (-44.94, -9.58)	-38.61 (-50.52, -17.02)	-41.16 (-54.05, -27.39)	-27.28 (-77.76, 6.41)
<b>Rosuvastatin</b>	-29.03 (-52.01, -8.91)	-61.49 (-77.06, -47.58)	-72.14 (-100.20, -54.28)	-87.75 (-113.9, -55.32)	---
<b>Simvastatin</b>	---	-49.48 (-67.77, -30.16)	-56.93 (-72.62, -40.93)	-60.26 (-83.73, -44.15)	-81.94 (-103.90, -53.73)

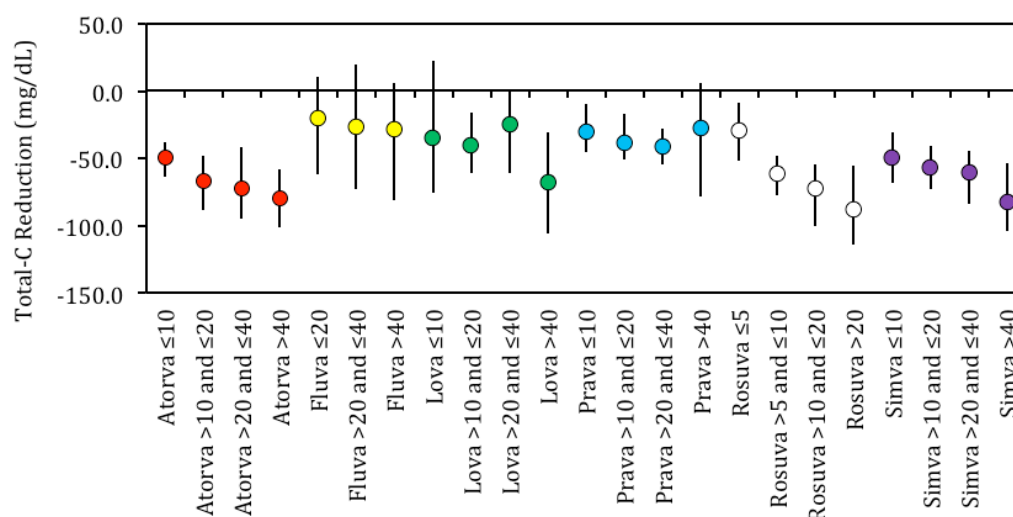
**(C)**

	≤5 mg/day	>5 and ≤10 mg/day	>10 and ≤20 mg/day	>20 and ≤40 mg/day	>40 mg/day
<b>Atorvastatin</b>	---	2.01 (-2.89, 6.41)	2.38 (-4.47, 7.76)	1.88 (-6.57, 10.35)	2.58 (-4.51, 8.78)
<b>Fluvastatin</b>	---	---	1.03 (-10.77, 12.58)	1.33 (-14.28, 16.65)	0.27 (-14.22, 16.23)
<b>Lovastatin</b>	---	1.48 (-17.17, 19.72)	1.76 (-8.8, 10.52)	0.36 (-10.15, 10.89)	3.00 (-10.16, 16.47)
<b>Pravastatin</b>	---	1.23 (-9.43, 11.65)	1.1 (-6.93, 8.81)	2.81 (-3.77, 7.30)	-1.63 (-21.24, 16.61)
<b>Rosuvastatin</b>	2.15 (-8.81, 10.40)	3.16 (-2.81, 9.79)	2.16 (-5.94, 12.03)	4.91 (-8.24, 19.86)	---
<b>Simvastatin</b>	---	2.39 (-7.37, 8.89)	1.79 (-4.25, 7.66)	2.77 (-5.3, 11.43)	1.69 (-5.32, 10.56)

\* Estimates shown are mean changes from baseline (mean, 95% CrI) in serum lipid concentrations as compared to control treatment for (A) LDL cholesterol; (B) Total cholesterol; and (C) HDL Cholesterol.

Considering Total cholesterol reduction, except for lovastatin and pravastatin, there was a general linear dose-response relationship for reducing Total cholesterol from baseline as compared to control (Figure 4.5). Fluvastatin at  $\leq 20$  mg/day (-19.82 mg/dL, 95% CrI: -61.95, 10.99 mg/dL), fluvastatin between  $>20$  and  $\leq 40$  mg/day (-26.27, 95% CrI: -72.20, 20.00 mg/dL), fluvastatin at  $>40$  mg/day (-28.41 mg/dL, 95% CrI: -80.73, 5.70 mg/dL), lovastatin at  $\leq 10$  mg/day (-34.66 mg/dL, 95% CrI: -75.46, 22.64 mg/dL), and pravastatin at  $>40$  mg/day (-27.28 mg/dL, 95% CrI: -77.76, 6.41 mg/dL) did not have adequate evidence to demonstrate superiority over control treatment in terms of lowering pretreatment Total cholesterol levels (Table 4.3). Highest reductions occurred with atorvastatin at  $>40$  mg/day (-79.22 mg/dL, 95% CrI: -101.2, -57.75), rosuvastatin between  $>10$  and  $\leq 20$  mg/day (-72.14 mg/dL, 95% CrI: -100.2, -54.28 mg/dL), rosuvastatin between  $>20$  and  $\leq 40$  mg/day (-87.75 mg/dL, 95% CrI: -113.9, -55.32 mg/dL), and simvastatin at  $>40$  mg/day (-81.94 mg/dL, 95% CrI: -103.90, -53.73 mg/dL).

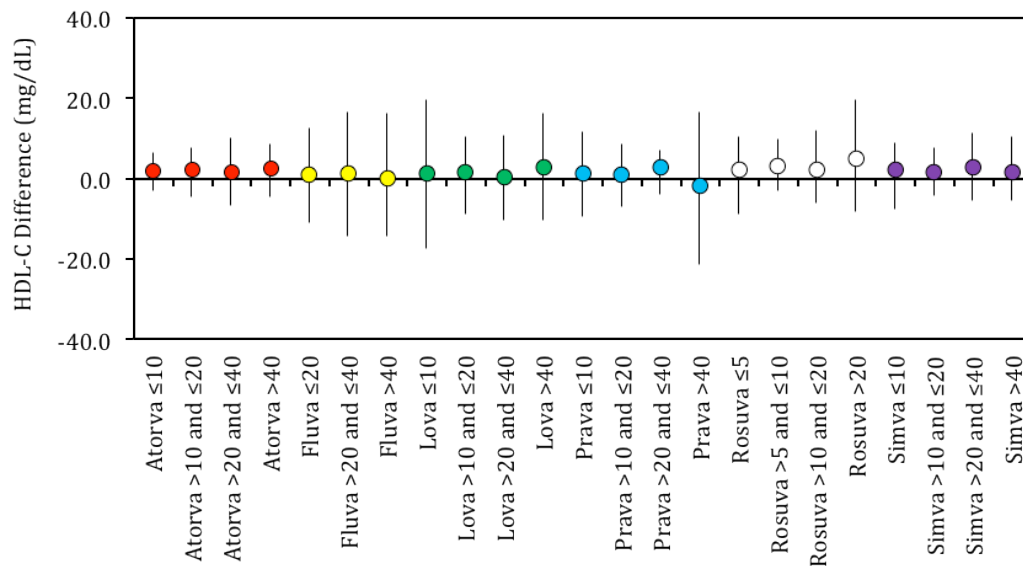
**Figure 4.5** – Dose-comparative relative effects of statins on serum Total cholesterol levels.\*



\* Estimates shown are mean changes from baseline (mean, 95% CrI) in serum Total cholesterol concentrations as compared to control treatment. Total-C: total cholesterol, atorva: atorvastatin, fluva: fluvastatin, lova: lovastatin, prava: pravastatin, rosuva: rosuvastatin, simva: simvastatin.

Statin-dose combinations resulted in only modest increases in baseline HDL cholesterol levels, and were not statistically significantly better than control treatment due to considerable uncertainty around the point estimates (Table 4.3). Higher doses of statins were not associated with greater increases in baseline HDL cholesterol concentrations (Figure 4.6).

**Figure 4.6** – Dose-comparative relative effects of statins on serum HDL cholesterol levels.\*

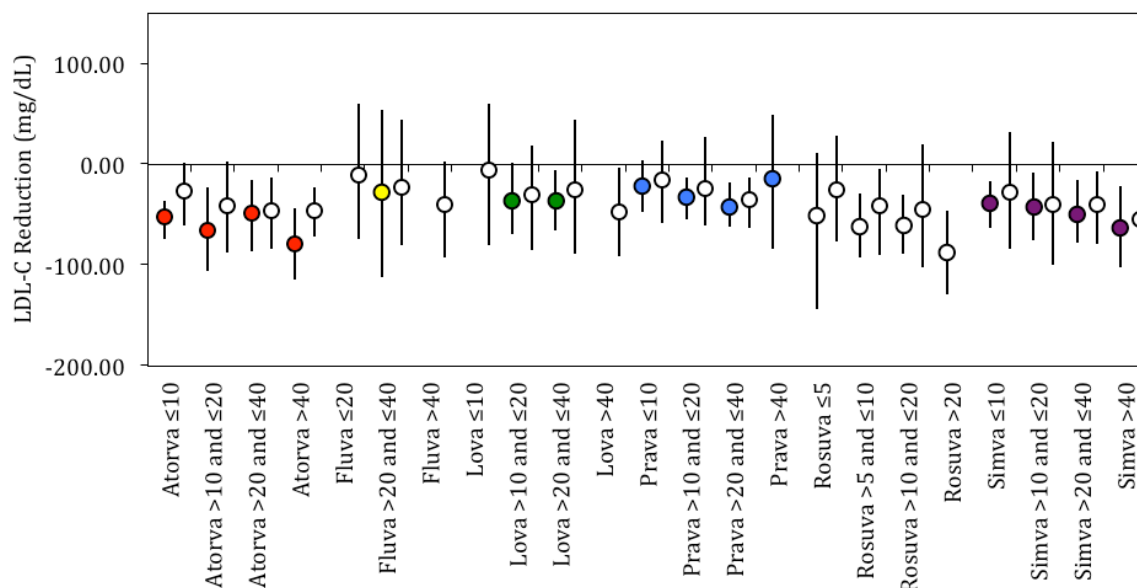


\* Estimates shown are mean changes from baseline (mean, 95% CrI) in serum HDL cholesterol concentrations as compared to control treatment. HDL-C: high-density lipoprotein cholesterol, atorva: atorvastatin, fluva: fluvastatin, lova: lovastatin, prava: pravastatin, rosuva: rosuvastatin, simva: simvastatin.

#### 4.3.1 Dose-comparative Effects of Statins in Primary and Secondary Prevention Populations

Figure 4.7 shows the dose-comparative effects of individual statins on pretreatment LDL cholesterol levels in primary and secondary prevention populations separately. Generally, higher statin doses were associated with greater relative reductions in pretreatment LDL cholesterol levels but this dose-response relationship was not as apparent as in the base-case analysis including all populations, which was primarily attributable to the fewer data points available for this analysis. With greatly overlapping 95% CrIs, there was no clear difference between the LDL cholesterol reducing effects of individual statins between populations with and without coronary heart disease at baseline (Table 4.4).

**Figure 4.7** – Sub-group analysis results: Dose-comparative relative effects of statins on serum LDL cholesterol levels.\*



\* Estimates shown are mean changes from baseline (mean, 95% CrI) in serum HDL cholesterol concentrations as compared to control treatment. Results are provided separately for primary prevention (in color) and secondary prevention (in white) populations. LDL-C: low-density lipoprotein cholesterol, atorva: atorvastatin, fluva: fluvastatin, lova: lovastatin, prava: pravastatin, rosuva: rosuvastatin, simva: simvastatin.

**Table 4.4** – Sub-group analysis results: Dose-comparative relative effects of statins on serum LDL cholesterol levels.\*

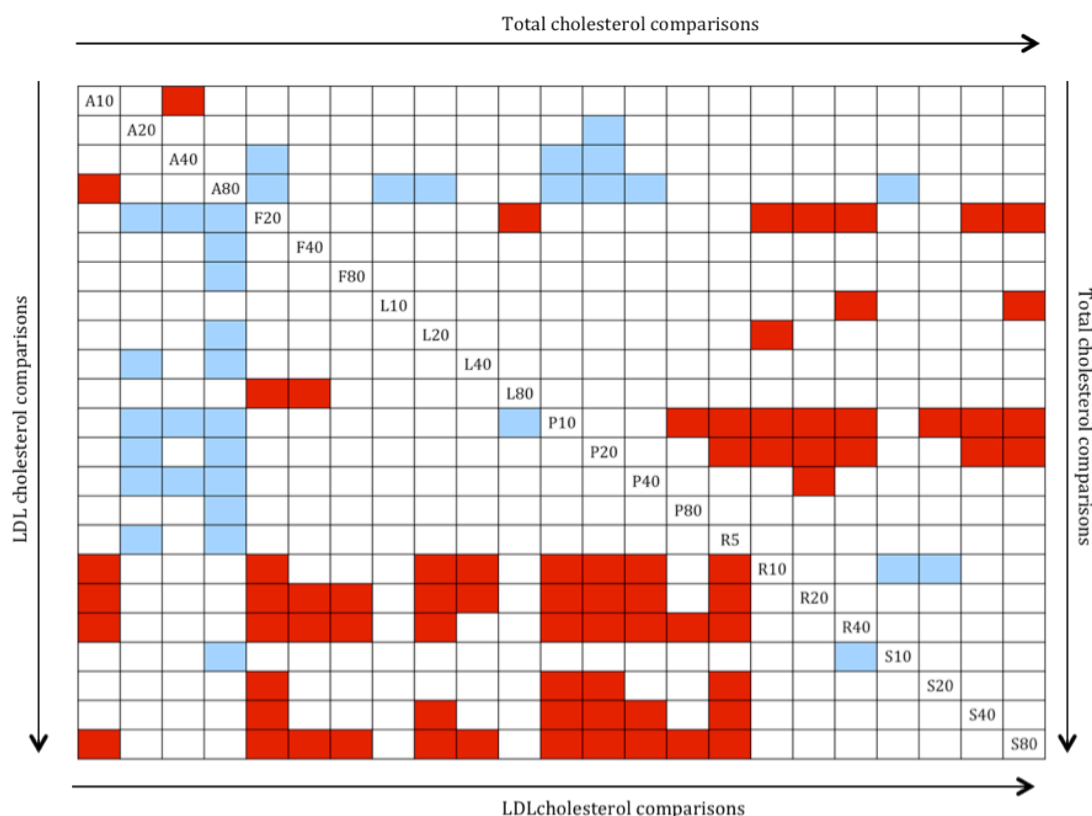
	≤5 mg/day	>5 and ≤10 mg/day	>10 and ≤20 mg/day	>20 and ≤40 mg/day	>40 mg/day
<b>Atorvastatin</b>	---	-52.67 (-68.02, -30.38) <i>-26.70 (-54.77, 7.84)</i>	-65.89 (-108.40, -24.86) <i>-41.87 (-86.31, 4.74)</i>	-49.20 (-82.73, -11.80) <i>-47.05 (-80.03, -8.96)</i>	-78.93 (-113.70, -42.78) <i>-46.63 (-69.92, -20.98)</i>
<b>Fluvastatin</b>	---	---	--- <i>-10.99 (-81.65, 53.14)</i>	-29.16 (-111.80, 54.29) <i>-23.93 (-91.09, 33.15)</i>	--- <i>-40.45 (-83.12, 11.79)</i>
<b>Lovastatin</b>	---	--- <i>-6.41 (-72.46, 67.64)</i>	-37.36 (-75.61, -4.38) <i>-31.07 (-80.46, 23.62)</i>	-37.09 (-67.64, -7.56) <i>-26.03 (-96.05, 37.84)</i>	--- <i>-47.45 (-91.44, -3.12)</i>
<b>Pravastatin</b>	---	-21.98 (-47.39, 3.25) <i>-16.35 (-55.80, 25.71)</i>	-33.75 (-53.73, -12.83) <i>-24.11 (-74.84, 13.17)</i>	-42.67 (-66.78, -22.31) <i>-35.22 (-56.73, -6.13)</i>	-15.03 (-78.11, 55.22) <i>-26.22 (-80.22, 25.15)</i>
<b>Rosuvastatin</b>	-51.40 (-113.10, 41.55) ---	-62.29 (-95.24, -31.68) <i>-41.71 (-78.07, 7.31)</i>	-61.58 (-92.33, -33.96) ---	-88.20 (-130.00, -47.17) <i>-45.50 (-109.90, 12.62)</i>	--- ---
<b>Simvastatin</b>	---	-39.71 (-62.65, -15.93) <i>-27.90 (-87.12, 28.20)</i>	-43.84 (-78.83, -11.27) <i>-40.90 (-103.80, 18.72)</i>	-50.72 (-85.43, -23.07) <i>-40.35 (-73.20, -1.33)</i>	-63.89 (-105.90, -25.42) <i>-55.61 (-107.80, -2.67)</i>

\* Estimates shown are mean changes from baseline (mean, 95% CrI) in serum LDL cholesterol concentrations as compared to control treatment. Italicized estimates are for the secondary prevention population.

When dose-comparative effects of individual statins were compared head-to-head, atorvastatin (at dosages >40 mg/day) and pravastatin (at dosages ≤20 mg/day) had the highest number of significant differences between comparators in reducing baseline LDL cholesterol concentrations (Figure 4.8). High-dose atorvastatin resulted in a large number of significant differences over comparator statin-dose combinations in reducing Total cholesterol. Rosuvastatin (at dosages >5 mg/day) and simvastatin (at dosages >40 mg/day) had the highest number of significant differences over comparators.

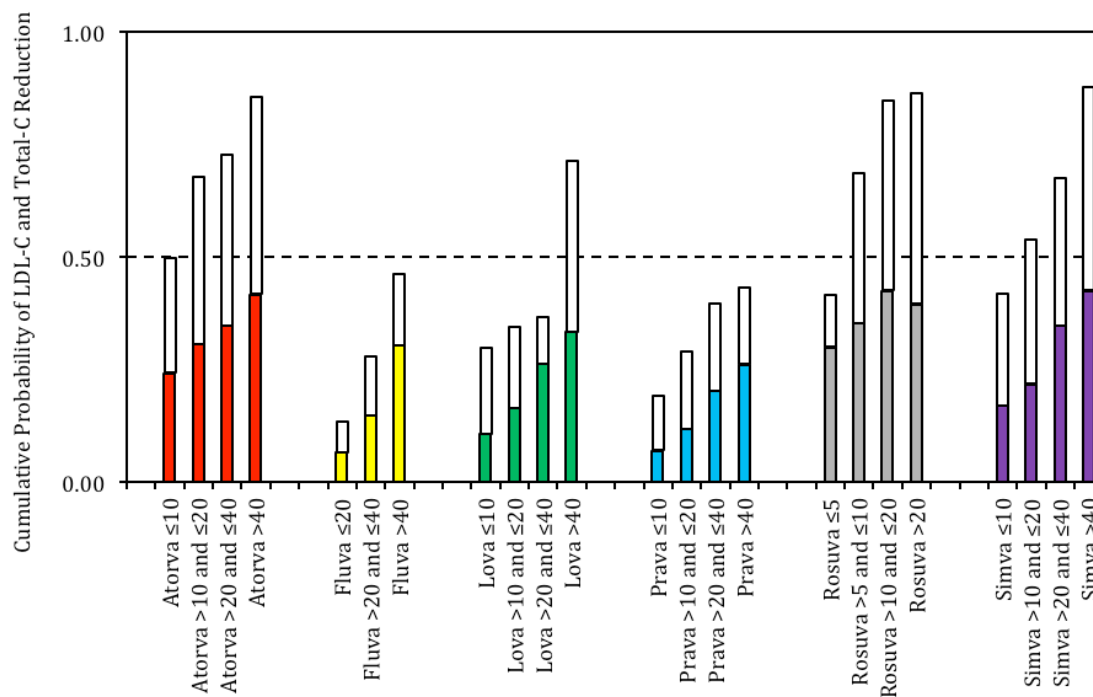
Figure 4.9 shows the ranking of individual statin-dose combinations in terms of lowering both baseline LDL and Total cholesterol concentrations. Ranking first, simvastatin (>40 mg/day), atorvastatin (>40 mg/day), and rosuvastatin (>10 mg/day) resulted in similar reductions in baseline LDL and Total cholesterol concentrations as compared to other statins. In second comparable group, atorvastatin at dosages between >10 and ≤40 mg/day, lovastatin at dosages >40 mg/day, and simvastatin between >20 and ≤40 mg/day resulted in comparable reductions in baseline cholesterol levels. Atorvastatin ≤10 mg/day, pravastatin >20 mg/day, rosuvastatin ≤5 mg/day, and simvastatin ≤10 mg/day ranked third. Remaining statin-dose combinations resulted in only modest reductions in baseline LDL and Total cholesterol concentrations.

**Figure 4.8** – Comparative LDL and Total cholesterol lowering effects of statin-dose combinations.\*



\* Top diagonal half of the table shows LDL cholesterol comparisons and the bottom diagonal half shows Total cholesterol comparisons. Every cell in the figure shows an estimate obtained from the network meta-analysis combining direct and indirect comparisons relevant for that particular comparison. Comparisons between drugs should be read from left to right. For LDL cholesterol comparisons, red denotes a 95% probability that the row-defining treatment is worse in reducing LDL cholesterol comparison than the column-defining treatment (e.g. atorvastatin at 10 mg/day results in statistically significantly less LDL cholesterol lowering as compared to atorvastatin at 80 mg/day). Blue denotes a 95% probability that the row-defining treatment is better in reducing LDL cholesterol than the column-defining treatment (e.g. atorvastatin at 20 mg/day results in statistically significantly more LDL cholesterol lowering as compared to fluvastatin at 20 mg/day). For Total cholesterol comparisons, red denotes a 95% probability that the column-defining treatment is worse than the row-defining treatment in reducing Total cholesterol. The opposite is the case for blue cells. LDL: low-density lipoprotein, A10: atorvastatin  $\leq 10$  mg/day; A20: atorvastatin  $> 10$  and  $\leq 20$  mg/day; A40: atorvastatin  $> 20$  and  $\leq 40$  mg/day; A80: atorvastatin  $> 40$  mg/day; F20: fluvastatin  $\leq 20$  mg/day; F40: fluvastatin  $> 20$  and  $\leq 40$  mg/day; F80: fluvastatin  $> 40$  mg/day; L10: lovastatin  $\leq 10$  mg/day; L20: lovastatin  $> 10$  and  $\leq 20$  mg/day; L40: lovastatin  $> 20$  and  $\leq 40$  mg/day; L80: lovastatin  $> 40$  mg/day; P10: pravastatin  $\leq 10$  mg/day; P20: pravastatin  $> 10$  and  $\leq 20$  mg/day; P40: pravastatin  $> 20$  and  $\leq 40$  mg/day; P80: pravastatin  $> 40$  mg/day; R5: rosuvastatin  $\leq 5$  mg/day; R10: rosuvastatin  $> 5$  and  $\leq 10$  mg/day; R20: rosuvastatin  $> 10$  and  $\leq 20$  mg/day; R40: rosuvastatin  $> 20$  mg/day; S10: simvastatin  $\leq 10$  mg/day; S20: simvastatin  $> 10$  and  $\leq 20$  mg/day; S40: simvastatin  $> 20$  and  $\leq 40$  mg/day; S80: simvastatin  $> 40$  mg/day.

**Figure 4.9** – Dose-comparative ranking and equivalence of statins in terms of both LDL and Total cholesterol reduction.\*

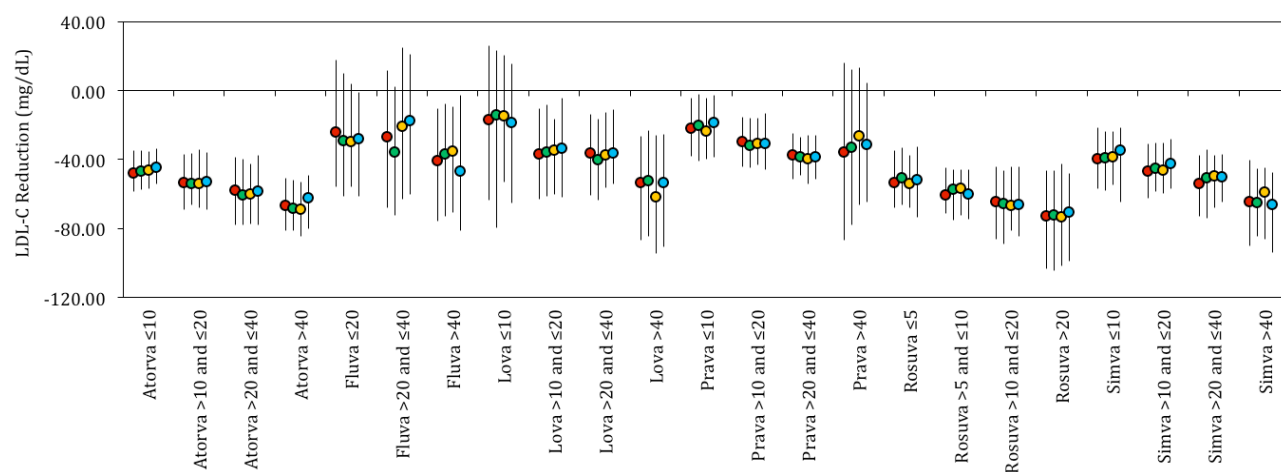


\* Estimates shown are based on the surface under the cumulative ranking plots by combining LDL cholesterol (bottom-half of the stacked bars in color) and Total cholesterol (top-half of the stacked bars in white) reducing effects of individual statins. Statin-dose combinations are ranked out of a total of 1.0 (0.5 for LDL cholesterol and 0.5 for Total cholesterol). LDL-C: low-density lipoprotein cholesterol, Total-C: total cholesterol, atorva: atorvastatin, fluva: fluvastatin, lova: lovastatin, prava: pravastatin, rosuva: rosuvastatin, simva: simvastatin.

#### 4.3.2 Investigation of Heterogeneity and Inconsistency in the Network Meta-analysis

When investigated qualitatively, study-level mean age of individuals appeared to have a modest effect on the reduction of pretreatment LDL cholesterol concentrations, with older individuals experiencing greater relative reductions in baseline LDL cholesterol concentrations as compared to younger individuals. According to the meta-regression analyses, baseline mean age ( $\beta = 0.54$ , 95% CI: -0.76, 2.13) and publication year ( $\beta = -0.37$ , 95% CI: -1.47, 0.96) did not explain heterogeneity in the analysis (Figure 4.10). The effect of baseline mean LDL cholesterol concentration was marginally statistically significant in the meta-regression analysis ( $\beta = -0.23$ , 95% CI: -0.49, -0.05) but its impact on the reduction of pretreatment LDL cholesterol concentrations were not materially different (Table 4.5).

**Figure 4.10** – Sensitivity of base-case network meta-analysis findings to meta-regression analyses.\*



\* Estimates shown are mean changes and 95% credible intervals in pretreatment LDL cholesterol concentrations as compared to control treatment. Base-case results are shown in red, while the analysis adjusting for mean age of patients at baseline is shown in green, the analysis adjusting for the mean LDL concentration at baseline is shown in yellow, and the analysis adjusting for publication year is shown in blue. LDL-C: low-density lipoprotein cholesterol, atorva: atorvastatin, fluva: fluvastatin, lova: lovastatin, prava: pravastatin, rosuva: rosuvastatin, simva: simvastatin.

**Table 4.5** – Sensitivity of base-case network meta-analysis findings to meta-regression analyses.\*\*

	≤5 mg/day	>5 and ≤10 mg/day	>10 and ≤20 mg/day	>20 and ≤40 mg/day	>40 mg/day
<b>Atorvastatin</b>	---	-47.77 (-58.56, -34.58) <i>-47.06 (-58.11, -34.92)*</i> <i>-46.51 (-57.09, -35.28)§</i> <i>-44.82 (-54.43, -33.53)¶</i>	-53.79 (-69.2, -36.99) <i>-53.87 (-66.36, -36.44)*</i> <i>-54.23 (-68.31, -34.11)§</i> <i>-53.05 (-68.99, -35.67)¶</i>	-57.76 (-78.43, -38.75) <i>-60.48 (-78.19, -39.94)*</i> <i>-59.98 (-77.95, -42.71)§</i> <i>-58.34 (-78.28, -37.45)¶</i>	-66.69 (-81.58, -50.93) <i>-68.26 (-81.65, -51.87)*</i> <i>-68.75 (-84.8, -53.15)§</i> <i>-62.23 (-80.19, -49.08)¶</i>
<b>Fluvastatin</b>	---	---	-24.42 (-56.2, 17.56) <i>-29.09 (-61.73, 9.94)*</i> <i>-29.94 (-55.78, 4.12)§</i> <i>-28.29 (-61.35, -0.764)¶</i>	-27.19 (-68.39, 11.74) <i>-35.90 (-72.99, 2.10)*</i> <i>-20.67 (-63.05, 24.95)§</i> <i>-17.74 (-60.6, 20.87)¶</i>	-40.72 (-75.84, -10.53) <i>-37.18 (-73.15, -7.50)*</i> <i>-35.32 (-71.24, -9.33)§</i> <i>-47.07 (-81.33, -2.51)¶</i>
<b>Lovastatin</b>	---	-16.94 (-63.78, 26.03) <i>-14.04 (-80.12, 23.22)*</i> <i>-14.82 (-53.09, 20.58)§</i> <i>-18.82 (-65.06, 15.07)¶</i>	-37.09 (-63.03, -10.40) <i>-35.55 (-61.35, -8.08)*</i> <i>-34.83 (-60.6, -16.46)§</i> <i>-33.72 (-61.76, -4.04)¶</i>	-36.43 (-60.68, -13.50) <i>-40.49 (-63.51, -16.25)*</i> <i>-37.75 (-56.45, -12.54)§</i> <i>-36.17 (-54.79, -11.20)¶</i>	-53.55 (-86.65, -26.32) <i>-52.47 (-84.88, -23.00)*</i> <i>-61.57 (-94.69, -26.07)§</i> <i>-53.54 (-90.85, -25.26)¶</i>
<b>Pravastatin</b>	---	-22.17 (-38.66, -4.50) <i>-20.42 (-41.16, -1.98)*</i> <i>-23.80 (-40.18, -4.57)§</i> <i>-18.68 (-39.34, -2.86)¶</i>	-29.70 (-44.64, -15.53) <i>-31.69 (-45.11, -16.18)*</i> <i>-30.75 (-43.46, -15.95)§</i> <i>-30.64 (-46.23, -13.10)¶</i>	-37.41 (-51.20, -24.57) <i>-38.34 (-49.34, -26.75)*</i> <i>-39.77 (-54.6, -26.06)§</i> <i>-38.77 (-51.96, -25.98)¶</i>	-35.97 (-87.03, 16.30) <i>-32.9 (-78.24, 12.34)*</i> <i>-26.61 (-66.43, 13.58)§</i> <i>-31.32 (-65.01, 4.33)¶</i>
<b>Rosuvastatin</b>	-53.32 (-67.71, -34.45) <i>-50.64 (-66.07, -32.85)*</i> <i>-53.88 (-67.94, -37.33)§</i> <i>-52.13 (-73.74, -32.44)¶</i>	-60.62 (-71.38, -44.81) <i>-57.48 (-75.15, -45.61)*</i> <i>-56.74 (-72.41, -45.51)§</i> <i>-60.02 (-74.75, -45.65)¶</i>	-64.32 (-85.90, -43.86) <i>-65.48 (-89.11, -46.19)*</i> <i>-66.68 (-81.57, -44.28)§</i> <i>-66.13 (-84.55, -44.01)¶</i>	-72.72 (-103.40, -46.26) <i>-72.31 (-105, -46.49)*</i> <i>-73.36 (-101.9, -42.22)§</i> <i>-70.56 (-99.28, -48.25)¶</i>	---
<b>Simvastatin</b>	---	-39.82 (-57.06, -21.58) <i>-39.30 (-58.15, -23.53)*</i> <i>-38.83 (-55.25, -23.89)§</i> <i>-34.82 (-64.83, -21.22)¶</i>	-47.00 (-62.45, -30.90) <i>-45.29 (-58.76, -30.38)*</i> <i>-46.25 (-59.89, -30.24)§</i> <i>-42.50 (-56.73, -27.93)¶</i>	-54.26 (-72.96, -37.46) <i>-50.91 (-74.70, -34.43)*</i> <i>-49.85 (-68.44, -37.51)§</i> <i>-50.04 (-65.34, -37.19)¶</i>	-64.50 (-90.27, -40.10) <i>-65.04 (-84.83, -45.12)*</i> <i>-59.02 (-86.17, -44.65)§</i> <i>-66.08 (-94.15, -47.52)¶</i>

\*\* Estimates shown are mean changes and 95% credible intervals in pretreatment LDL cholesterol concentrations as compared to control treatment. In addition to base-case results, findings from the three sets of meta-regression analyses are provided. Meta-regression results are *italicized*.

\* Meta-regression analysis adjusting for mean baseline age.

§ Meta-regression analysis adjusting for mean baseline LDL cholesterol concentration.

¶ Meta-regression analysis adjusting for publication year.

There was no detectable inconsistency between direct and indirect estimates when results of direct and mixed comparisons were visually inspected for potential discrepancies. Relative reductions from baseline LDL cholesterol concentrations were similar for all statin-dose combinations and the 95% CrIs of direct-only and mixed (combination of direct and indirect) estimates greatly overlapped for all comparisons. Between-study heterogeneity in the network meta-analysis for the primary outcome of LDL cholesterol reduction from baseline was low (sd: 1.71, 95% CrI: 0.25, 4.64).

#### **4.6 Summary of Findings**

This network meta-analysis of 256,827 individuals provided comprehensive evidence on the dose-comparative effects of individual statins on serum lipid concentrations. Overall, high-dose statins were associated with greater reductions in pretreatment LDL cholesterol and Total cholesterol concentrations as compared to low-dose regimens. In terms of increasing HDL cholesterol, all statin-dose combinations failed to result in clinically and statistically meaningful increases in pretreatment HDL cholesterol levels and higher doses were not associated with better HDL cholesterol improvements.

When individual statins were compared head-to-head, several statins appeared to outperform other statins in reducing serum LDL and Total cholesterol concentrations. In this network meta-analysis, atorvastatin, rosuvastatin and simvastatin ranked first in terms of reducing serum LDL and Total cholesterol as compared to other statins. High-dose formulations of atorvastatin, rosuvastatin, and simvastatin were broadly equivalent. Fluvastatin, lovastatin, and pravastatin, however, were associated with significantly less reductions in pretreatment LDL cholesterol and Total cholesterol concentrations relative to other statins. Low-dose regimens of fluvastatin and lovastatin did not lower pretreatment cholesterol levels over and above the reduction observed in control treatment.

Dose-comparative effects of individual statins on lowering LDL cholesterol were not different between those with and without coronary heart disease at baseline. According to meta-regression analyses, LDL cholesterol lowering effects of individual statins were not impacted by differences across trials in terms of baseline mean age and publication year. Pretreatment LDL cholesterol concentrations had a marginally statistically significant effect on LDL cholesterol changes from baseline.

This analysis was the first to quantitatively evaluate the dose-comparative effects of different statins on serum lipids across all populations, and for primary and secondary prevention

populations separately. Previous comprehensive reviews such as the Drug Class Review did not perform statistical analyses, which considerably hindered the validity of inferences that could be made on the basis of implicit indirect comparisons. The statin dose conversion/equivalence tables that stemmed from previous reviews did not take into account the statistical uncertainty around the dose-comparative effects of statins. As a result, existing dose conversion tables give the false impression that prescribers could expect narrow ranges of LDL cholesterol reductions at various statin doses.

Based on the findings presented in this chapter, a revised ‘Statin Prescribing Reference’ table was developed, as shown below (Table 4.6). This table reports the statistically equivalent doses of statins and the percent LDL cholesterol changes that can be expected when prescribing them. Also included are statements about the consistency of the evidence associated with the preferred agents, which reflect the variability (and uncertainty) in the evidence base.

**Table 4.6 – Statin Prescribing Reference Table.**

<b>Statin-dose</b>	<b>Target Reduction</b>	<b>Estimated LDL-C reduction from pretreatment levels</b>
Atorva >40 mg/day Rosuva >10 mg/day Simva >40 mg/day	High	Prescribers can expect an approximately 45% reduction from pretreatment LDL cholesterol levels with 95% of reductions ranging from 23% to 66%.  Evidence is most consistent for atorvastatin. This agent should be preferred to initiate therapy.
Atorva ≤40 mg/day Fluva >40 mg/day Lova >20 mg/day Prava >20 mg/day Rosuva ≤10 mg/day Simva >10 and ≤40 mg/day	Medium	Prescribers can expect an approximately 38% reduction from pretreatment LDL cholesterol levels with 95% of reductions ranging between 6% and 61%.  The uncertainty is due in large part to the variability in the evidence base for fluvastatin and pravastatin (at their highest doses).  Evidence is most consistent for atorvastatin, rosuvastatin, and simvastatin. These agents should be preferred to initiate therapy.
Fluva ≤40 mg/day Lova ≤20 mg/day Prava ≤20 mg/day Simva ≤20 mg/day	Low	Prescribers can expect an approximately 20% reduction from pretreatment LDL cholesterol levels. In 95% of the cases, patients are estimated to experience changes between 10% increase* and 42% decrease in their baseline LDL cholesterol concentrations.  *Lowest doses of fluvastatin and lovastatin may at times not result in reductions in baseline LDL cholesterol levels.  Evidence is most consistent for pravastatin and simvastatin. These agents should be preferred to initiate therapy.

The findings of this analysis are novel and differ from previous reviews in important ways. First, the traditionally considered “more powerful” statins – notably rosuvastatin which is not generic,

and atorvastatin which has recently been released as a generic – were not found to be statistically superior to simvastatin in their maximum LDL cholesterol lowering doses (this has been an assumption in the literature and clinical practice). Second, the extent to which some statins lower pretreatment LDL cholesterol levels appeared to be less pronounced in this review compared to earlier estimates. This was particularly the case for atorvastatin and rosuvastatin at high doses. For instance, according to previous analyses, high-dose atorvastatin (at 80 mg/day) lowers pretreatment LDL cholesterol levels by 55%<sup>148,340,342</sup> (and 60% according to manufacturer's prescribing information). This network meta-analysis found that high-dose atorvastatin lowers baseline LDL cholesterol concentrations by an estimated 45% (95% CrI: 35%, 54%). Similarly, according to manufacturer's prescribing information, high-dose rosuvastatin lowers pretreatment LDL cholesterol levels by 63%. However, the findings of this network meta-analysis suggested that high-dose rosuvastatin resulted in a 46% mean reduction from baseline, which was associated with considerable uncertainty (95% CrI: 23%, 66%). This difference was also observed for other statin-dose combinations: 20 mg/day of fluvastatin (-22% per prescribing information vs. -11% in this analysis), 20 mg/day of pravastatin (-32% per prescribing information vs. -22% in this analysis). LDL cholesterol-lowering effects of simvastatin according to this network meta-analysis appeared consistent with previous findings.

This difference can be attributed to three main factors. First, previous assessments of dose-comparative effects of statins were based on small studies, which tend to evaluate highly-selected patients in strictly controlled environments, which may not be representative of the conditions in actual clinical practice. The systematic review that formed the basis of the network meta-analysis reported in this chapter excluded trials that included fewer than 50 individuals per trial arm. As a result, 123 trials that were included in the review by Law and colleagues were not eligible for inclusion in this network meta-analysis.<sup>148</sup>

Second, unlike previous reviews, this systematic review included trials with individuals regardless of their baseline LDL cholesterol concentrations. As a result, this systematic review included trials such as TNT (Treating to New Targets) during which patients receiving atorvastatin at 80 mg/day experienced an estimated 21% reduction in pretreatment LDL cholesterol concentrations.<sup>343</sup> This was justified based on the findings of previous reviews that showed that relative reductions are not impacted by baseline LDL cholesterol levels.<sup>335</sup>

Third, earlier reviews excluded trials with titration designs. Titration designs allowing clinicians to increase the dose of statin therapy to achieve target reductions, also known as the 'treat-to-

target' model, continues to be the most common method of managing patients with elevated LDL cholesterol levels. Accordingly, this review included information from titration design trials such as IDEAL (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering), which compared atorvastatin (at 80 mg/day) and simvastatin (starting at 20 mg/day, average dose throughout trial: 24 mg/day).<sup>344</sup> When extracting data from titration trials for this systematic review, a careful approach was taken to accurately proportion patients into correct dose categories. Whenever possible, data from the fixed dosing period were used. If all patients were force-titrated to a given dosage, data from the final high-dose period were used. As an example, STAT (Simvastatin To Atorvastatin switch Trial) randomized patients to simvastatin 40 mg or atorvastatin 40 mg for 8 weeks, after which the atorvastatin dose was increased to 80 mg while the simvastatin dose remained the same.<sup>345</sup> Per the data extraction protocol for this systematic review, patients receiving atorvastatin in the STAT (whose LDL cholesterol levels went down by approximately 20%) were categorized as receiving a dose of 80 mg/day.

Given the Bayesian nature of the analysis, the extent of potential heterogeneity was not quantified using the common  $I^2$  statistic. Instead, the between-study heterogeneity was directly quantified, which was found to be low. In addition, every attempt was made to visually inspect potential discrepancies in the reported results across trials. The potential inconsistency between direct and mixed findings in the analysis was explored by comparing the 95% CrI of estimates obtained from analyses including only direct (head-to-head) trials and from those that combined direct trials with placebo-controlled trials. Also, meta-regression analyses were performed to evaluate whether potential heterogeneity or inconsistency could be explained by baseline LDL cholesterol levels across trials. This statistical exploration did not find evidence that baseline LDL cholesterol had an impact on the relative treatment effects.

The findings of this comparative analysis should be interpreted in light of its limitations. First, there are other important lipid outcomes, which should be evaluated in future analyses.<sup>346</sup> One such outcome is non-HDL cholesterol. Recent research, published after the work presented in this chapter was completed, showed that there is an association between non-HDL cholesterol levels with the risk of cardiovascular events among patients treated with statin therapy.<sup>347</sup> Second, as a network meta-analysis combining direct and indirect sources of evidence, it remains a possibility that potential imbalances in the occurrence of effect modifiers across the contrasts impacted the results, potentially confounding the comparative estimates between individual statins. However, this is unlikely given the large body of evidence that provided consistent estimates from a broadly representative group of individuals with different

characteristics across trials. In addition, meta-regression analyses did not find evidence that baseline LDL cholesterol levels had an impact on the relative treatment effects.

Despite these limitations, this review has important strengths. Based on 256,827 individuals in 181 randomized controlled trials, this network meta-analysis provides the most comprehensive evidence on the relative potency of individual statins in reducing LDL cholesterol and Total cholesterol, and increasing HDL cholesterol. It included evidence from both placebo-controlled and active-comparator trials, considerably broadening the evidence base included in previous reviews. Interestingly, it is the first network meta-analysis that includes more direct head-to-head trials than placebo-controlled trials in any type of meta-analysis,<sup>10</sup> which considerably strengthens the statistical inferences of the findings. Including titration design trials considerably improved the generalizability of the findings as titration better reflects common practice in cholesterol management. As a result of the inclusive approach taken for the systematic review, the findings of the network meta-analysis are generalizable to individuals in clinical practice. It included a broad range of patients and observed that the cholesterol-lowering effects of statins are consistent across age groups and populations with different comorbidity profiles.

In conclusion, this chapter reported the findings of the most comprehensive meta-analysis of the effect of statins on reductions in serum cholesterol concentrations, and one of the first to integrate direct head-to-head comparisons between individual statins. Overall, high-dose statins were associated with greater reductions in pretreatment LDL cholesterol and Total cholesterol concentrations as compared to low-dose regimens confirming a dose-response relationship. When individual statins were compared head-to-head, several statins appeared to outperform other statins in reducing serum LDL cholesterol and Total cholesterol concentrations. Atorvastatin, rosuvastatin and simvastatin ranked first in terms of reducing serum LDL cholesterol and Total cholesterol as compared to the other statins in the analysis, and were considered statistically equivalent. The LDL cholesterol reducing effects of some statins appear less pronounced than the findings of previous meta-analyses.

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<sup>10</sup> This is likely a reflection of the randomized controlled trial evidence base for statins, which includes a large number of head-to-head trials.

## Chapter 5

### Comparative Benefits of Individual Statins\*

The objective of cholesterol-lowering therapy with statin drugs is to lower the risk of mortality and other clinically meaningful outcomes such as major coronary events (e.g., heart attacks) and major cerebrovascular events (e.g., strokes). As the number of individuals eligible for statin therapy continues to increase both in primary and secondary prevention, an important question that warrants further investigation is the comparative effects of individual statins. Whether individual statins vary in terms of their effect on total mortality and clinical endpoints when compared head-to-head at similar doses is unclear and has not been studied in a comprehensive manner in previous meta-analyses. Information regarding the relative clinical value of different statins in primary and secondary prevention of coronary heart disease is needed to better inform patients, prescribers, and other healthcare decision makers.

A number of prior meta-analyses explored the comparative benefits of individual statins in terms of total mortality and clinical endpoints – each with important limitations. The earliest example, the analysis by Zhou and colleagues (2006), aptly titled “are all statins created equal?”, performed an indirect comparison to address this question.<sup>105</sup> This analysis focused on atorvastatin, pravastatin, and simvastatin based on published randomized placebo-controlled trials. Trials were eligible for inclusion if they enrolled more than 1,000 individuals, and had at least a year of follow-up. Based on this limited sample of relevant trials (eight trials including 63,143 individuals), authors did not find a statistically significant difference between individual statins in reducing major coronary events. Similarly, there were no differences between

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\* Part of the work presented in this chapter was published with the following references:

Naci H, Brugts JJ, Fleurence R, Tsoi B, Toor H, Ades AE. Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. *Eur J Prev Cardiol*. 2013 Aug;20(4):641-57.

Naci H, Brugts JJ, Fleurence R, Ades AE. Comparative effects of statins on major cerebrovascular events: a multiple-treatments meta-analysis of placebo-controlled and active-comparator trials. *QJM*. 2013 Apr;106(4):299-306.

individual statins in terms of fatal and non-fatal strokes, cardiovascular deaths, and all-cause mortality. In a sensitivity analysis that included usual-care controls, however, atorvastatin appeared statistically significantly more effective than pravastatin (RR: 0.71, 95% CI: 0.56 to 0.90) and simvastatin (RR: 0.79, 95% CI: 0.63 to 0.99).

In 2008, Mills and colleagues performed an indirect treatment comparison of four statins for the primary prevention of cardiovascular mortality.<sup>257</sup> This analysis included 20 randomized placebo-controlled trials including 65,000 individuals. There were four trials of atorvastatin, three of fluvastatin, two of pravastatin, and 11 trials of pravastatin. The indirect comparison did not provide evidence that individual statins were different from each other in terms of reducing the risk for clinical outcomes that were evaluated in the primary prevention setting. In a later analysis published in 2011, Mills and colleagues undertook a more comprehensive network meta-analysis of six statins for the prevention of cardiovascular disease.<sup>348</sup> This analysis included 170,255 individuals from 76 randomized placebo-controlled trials and compared individual statins in terms of all-cause mortality and cardiovascular mortality. Similar to their earlier analysis, there were no statistically significant differences between individual statins.

In sum, earlier network meta-analyses that indirectly compared individual statins were limited to placebo-controlled trials and did not take into account evidence from a large number of active-comparator trials (previous network meta-analyses were based on existing systematic reviews, which were only based on placebo-controlled trials). Equally importantly, these analyses did not differentiate between primary and secondary prevention populations. Finally, previous network meta-analyses did not assess differences in dosages of individual statins across populations and did not compare statins at similar doses. In light of these limitations, a network meta-analysis was performed to synthesize the randomized trial evidence on statins as identified in the systematic review.

This chapter reports the findings of a comprehensive network meta-analysis that combines evidence from both placebo-controlled and active-comparator trials of statins on clinical endpoints. The overall effect of statins on all-cause mortality, major coronary events, and major cerebrovascular events across all populations, in addition to secondary and primary prevention of cardiovascular disease, are evaluated. The effects of individual statins head-to-head in these patient populations are compared, taking into account dose differences across the included set of trials.

## 5.1 Empirical Considerations

As outlined in Chapter 3 (*Evidence Review and Synthesis Methods*) separate traditional pair-wise meta-analyses and network meta-analyses were performed for all-cause mortality, major coronary events, and major cerebrovascular events. Traditional pair-wise meta-analyses were based on placebo-controlled trials whereas the network meta-analyses combined placebo-controlled and active-comparator trials. For each endpoint, three sets of analyses were conducted. First, to obtain an overall estimate of the effect of statins, all primary and secondary prevention trials were pooled in addition to trials with mixed patient populations. Subsequently, separate analyses were performed for the primary prevention and secondary prevention populations.

*Consideration of dose in the network meta-analysis:* For the base-case network meta-analysis, trials with high doses (80 mg/day for atorvastatin, fluvastatin, lovastatin, simvastatin, and  $\geq 40$  mg/day for rosuvastatin) were excluded and the benefits of statins were evaluated at broadly comparable LDL cholesterol-lowering doses. This was done to evaluate whether individual statins had different mortality and cardiovascular benefits irrespective of their LDL cholesterol-lowering effects. In a sensitivity analysis, trials that evaluated statins at high doses were also included. A dose-specific analysis explored the effects of individual statins at low, medium, and high doses separately. For the dose-specific analysis, doses were categorized as low ( $\leq 20$  mg/day), medium ( $>20$  mg/day  $\leq 40$  mg/day), and high ( $>40$  mg/day) for atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. A different categorization scheme was adopted for rosuvastatin given its considerably higher potency per mg as compared to other statins. For rosuvastatin, doses  $\leq 10$  mg/day were categorized as low,  $>10$  mg/day  $\leq 20$  mg/day as medium, and  $>20$  mg/day as high. This categorization of doses deviated from that used in Chapters 4 and 6 (which adopted a more granular breakdown of doses where all possible statin-dose combinations were considered separately) due to the small number of clinical events observed in the analyses presented in this chapter.

For the dose-specific analysis, each statin-dose combination was treated as a different treatment and no trends were fitted or assumed. All analyses were based on the total number of randomly assigned participants if the study authors did not perform intention-to-treat analyses.

*Ranking of statins in the network meta-analysis:* The probability that each statin was the most efficacious regimen was estimated by calculating the treatment effect for each statin compared

with the common comparator treatment, and counting the proportion of iterations of the Markov chain in which each drug had the highest treatment effect, the second highest, and so on. Rank probabilities were separately estimated for all-cause mortality, major coronary events, and major cerebrovascular events. Rankograms were developed to graphically present the distribution of ranking probabilities. Also, cumulative probability plots were developed for each outcome and the surface under the cumulative ranking line for each statin was estimated as described in Chapter 3 (*Evidence Review and Synthesis Methods*).<sup>324</sup> The surface area under the cumulative ranking line provided a numerical summary of the overall score for each statin for each outcome. Each statin was scored with points up to a maximum of 1.00, which was the weighted sum of scores separately estimated for all-cause mortality, major coronary events, and major cerebrovascular events.

*Assessment of heterogeneity and inconsistency in the network meta-analysis:* Whether potential heterogeneity and inconsistency across the evidence base could be explained by differences in trial publication year, baseline LDL cholesterol concentration, and baseline mean age of patients was investigated using meta-regression analyses. All meta-regression analyses were performed by allowing for a common treatment-covariate interaction for each statin compared to control, as described in Chapter 3.<sup>327</sup> In addition to the three study-level variables (trial publication year, baseline LDL cholesterol concentration, and baseline mean age of patients), an exploratory analysis investigated the association between baseline risk (odds of an event in the placebo arm of each trial) and treatment effect in the placebo-controlled trials of statins. Baseline risk reflected the risk of outcome event for a patient under the control condition and indicated average risk of patient in that trial if they were not treated. Exploration of baseline risk was considered important and necessary, as baseline risk of study population could modify the effect of intervention in a given trial.

To further explore any potential inconsistency between direct and indirect evidence, the ratio of relative effects for indirect versus direct evidence was calculated.<sup>329</sup> Inconsistency was defined as the disagreement between direct and indirect evidence with a 95% CI excluding 1.00.<sup>289</sup>

*Presentation of results:* First, the findings of the traditional pair-wise meta-analysis were presented along with estimates of heterogeneity in the pooled estimates of the identified placebo-controlled trials. Subsequently, the findings of the network meta-analysis which combined evidence from placebo-controlled and active-comparator trials were presented. This was followed by the presentation of meta-regression results which provided a statistical assessment of heterogeneity and inconsistency in the network meta-analysis. The results of

additional exploratory inconsistency analyses were provided in the *Appendix*, along with additional detailed results that formed the basis of the main results presented in this chapter.

*Goodness of fit:* As described in Chapter 3: *Evidence Review and Synthesis Methods*, the goodness of fit of the network meta-analysis models was examined using the total residual deviance (posterior mean of the deviance under a given model minus the deviance for the saturated model) and deviance information criterion (DIC). Model fit was considered to be satisfactory on the basis of both measures. In each model, the residual deviance was compared with the total number of data points in the dataset.

Assessment of model fit for the base-case network meta-analysis

	Effective number of parameters, pD	Total residual deviance	DIC
All-cause mortality	94	205	873
Major coronary events	78	143	737
Major cerebrovascular events	71	141	651

*Interpretation of results:* The results of the traditional pair-wise meta-analyses were reported in terms of odds ratios and 95% CIs. Given the Bayesian nature of network meta-analyses, the findings of these analyses were reported using odds ratios and 95% CrIs. In traditional pair-wise meta-analyses, the findings were considered ‘*statistically significant*’ when the 95% confidence interval did not include the null value 1.00. Adopting the emerging convention in reporting and interpreting the findings of Bayesian network meta-analyses, 95% CrIs that did not cross the null value of 1.00 were considered ‘significant’. Use of ‘significance’ in this way is consistent with the latest network meta-analyses that appeared in general medical journals.<sup>257</sup>

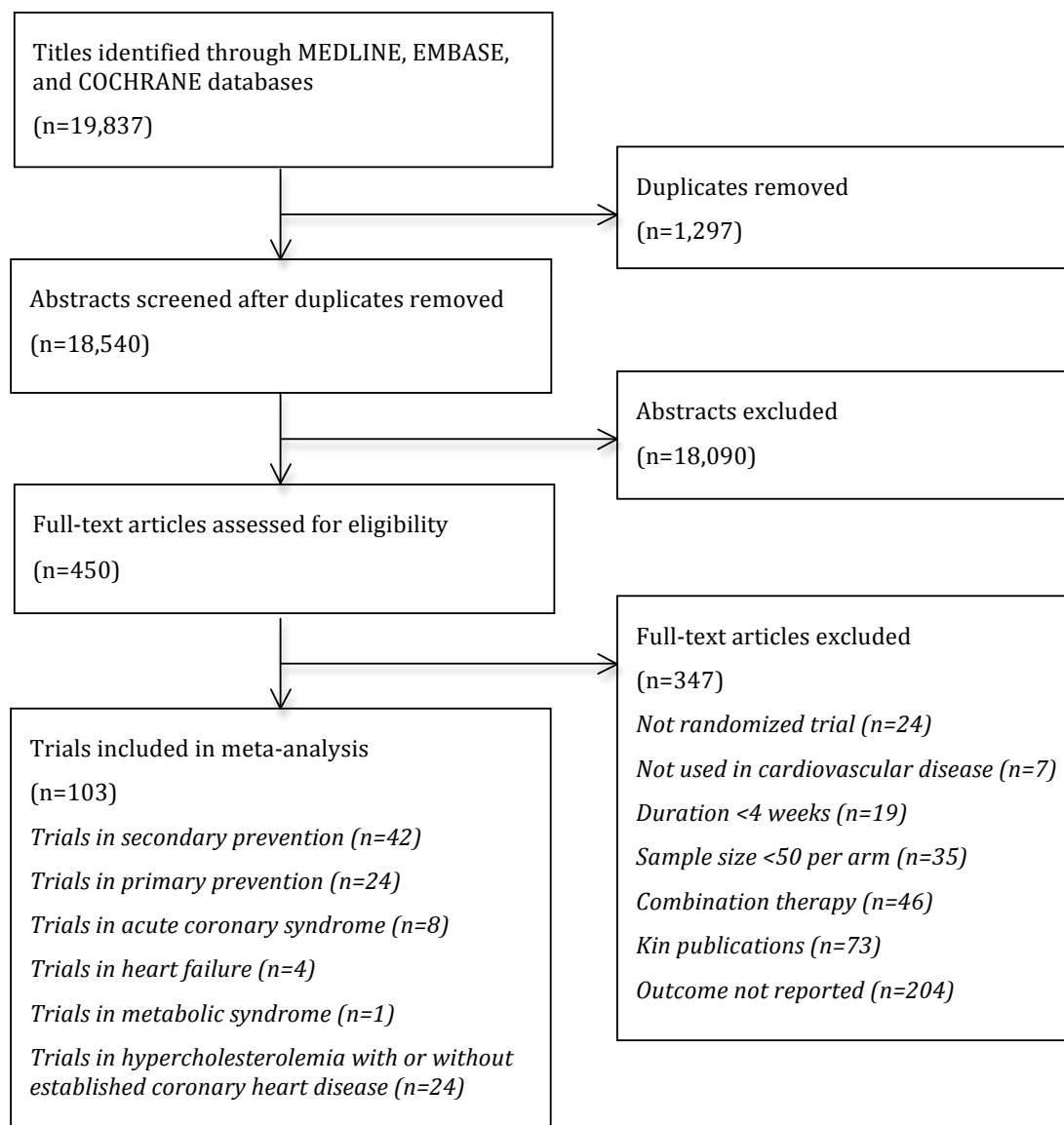
## 5.2 Systematic Review Findings

There were 103 randomized controlled trials in the systematic review and meta-analysis of total mortality and clinical outcomes (Figure 5.1). These trials included a total of 214,877 individuals. Overall, the average trial duration was 104 weeks (approximately 2 years). Fifty-two trials had a mean duration of one year or longer and participants in 24 trials were followed up for less than 6 months. Twenty trials were conducted in the primary prevention population compared with 42 trials in the secondary prevention population. The remaining 41 trials included participants with or without established cardiovascular disease. Among these, there were eight trials of

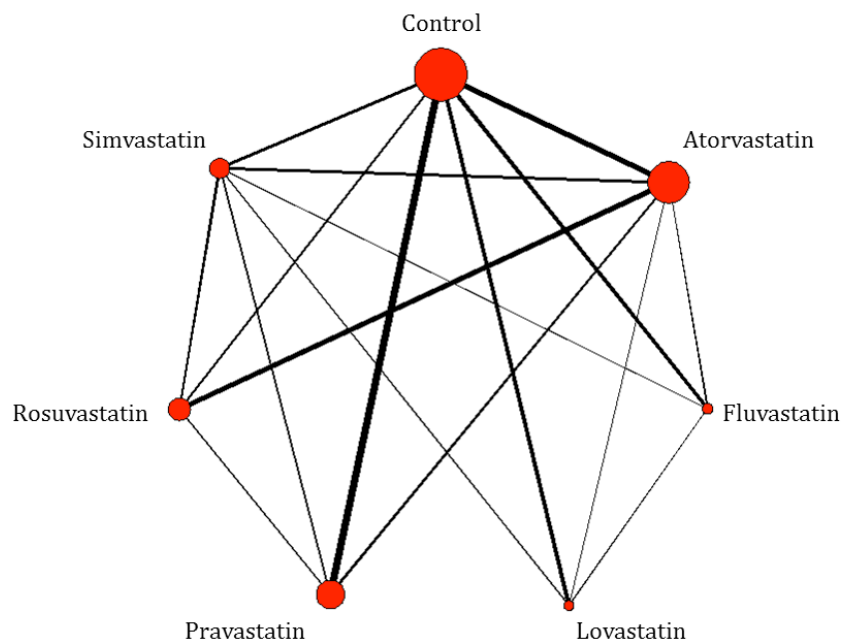
patients with acute coronary syndromes, four trials that primarily included participants with heart failure, and one trial with metabolic syndrome.

Figure 5.2 shows the network of eligible pair-wise comparisons for deaths and clinical outcomes (all-cause mortality, major coronary events, and major cerebrovascular events) in placebo-controlled and active-comparator trials of individuals across all populations. Of the 15 possible pair-wise comparisons between the six statins, 11 were available in the identified literature. No trial directly compared all six statins to each other in terms of clinical outcomes. The majority of the existing pair-wise comparisons were placebo-controlled trials (N=65). The remaining trials were two- or multi-arm active-comparator trials (N=38). Of these 38 active-comparator trials, four were two-arm or multi-arm active-comparator trials, and two were multi-arm trials including a placebo comparison. The frequency of direct head-to-head comparisons varied widely by statin. For instance, fluvastatin and lovastatin were primarily tested in placebo-controlled trials whereas rosuvastatin had more head-to-head comparisons than placebo-controlled trials.

**Figure 5.1** – Flow diagram of trial identification and selection.



**Figure 5.2** – Network of available comparisons for determining the comparative effects of individual statins on clinical benefit outcomes.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

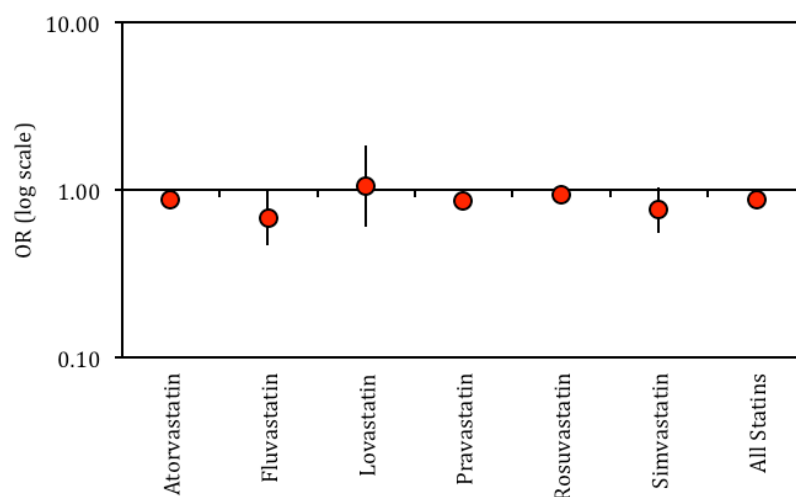
### 5.3 Outcome 1: All-Cause Mortality

#### 5.3.1 Benefits of Statins vs. Control: Findings of the Traditional Pair-wise Meta-analysis

In the traditional pair-wise meta-analysis of statin therapy vs. control across all populations, 169,615 participants contributed information on 12,398 deaths across 60 placebo-controlled trials (see the *Appendix* for trial-level results). There were 13 trials of atorvastatin providing information on 1,466 deaths among 27,159 individuals; six trials of fluvastatin with 120 deaths among 4,829 individuals; eight trials of lovastatin with 222 deaths among 17,356 individuals; 22 trials of pravastatin with 4,036 deaths among 58,653 individuals; five trials of rosuvastatin with 3,235 deaths among 31,997 individuals; and six trials of simvastatin with 3,319 deaths among 29,621 individuals.

Overall, as shown in Figure 5.3, statin therapy was associated with a reduction in all-cause mortality (OR: 0.87, 95% CI: 0.82, 0.92,  $I^2=22.6\%$ ) (see *Appendix* for trial-level results). Among statins, only fluvastatin (OR: 0.68, 95% CI: 0.47, 0.99,  $I^2=0.0\%$ ) and pravastatin (OR: 0.86, 95% CI: 0.80, 0.93,  $I^2=8.1\%$ ) were associated with a significant reduction in all-cause mortality compared with the control, while atorvastatin (OR: 0.88, 95% CI: 0.77, 1.01,  $I^2=15.2\%$ ), lovastatin (OR: 1.05, 95% CI: 0.60, 1.85,  $I^2=23.6\%$ ), rosuvastatin (OR: 0.93, 95% CI: 0.83, 1.05,  $I^2=33.6\%$ ), and simvastatin (OR: 0.76, 95% CI: 0.56, 1.04,  $I^2=66.4\%$ ) were not. According to contour-enhanced funnel plots, there was no evidence of differential effects between more precise and less precise trials according to contour-enhanced funnel plots (i.e., no evidence of small study effects) (see *Appendix*).

**Figure 5.3** – Effect of statins compared to control on all-cause mortality across all populations.\*



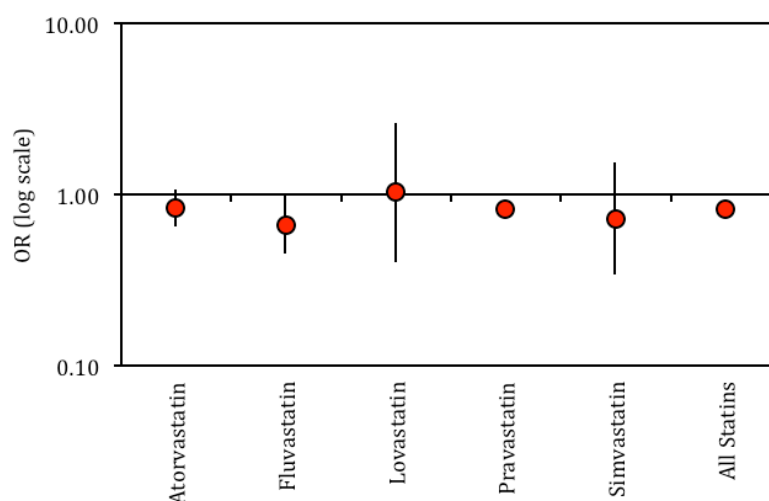
\* Estimates shown are ORs and 95% CIs.

In the secondary prevention population, 49,936 participants contributed information on 3,823 deaths across 32 placebo-controlled trials. There were six trials of atorvastatin providing information on 878 deaths among 11,945 individuals; four trials of fluvastatin with 109 deaths among 3,304 individuals; five trials of lovastatin with 20 deaths among 1,385 individuals; 13 trials of pravastatin with 2,339 deaths among 27,286 individuals; and four trials of simvastatin with 477 deaths among 6,016 individuals. There were no trials of rosuvastatin in this population.

Among individuals with established coronary artery disease, statin therapy was associated with a significant reduction in all-cause mortality (OR: 0.82, 95% CI: 0.75, 0.90,  $I^2=14.8\%$ ) (Figure

5.4). In this population, only pravastatin (OR: 0.82, 95% CI: 0.75, 0.90,  $I^2=0.0\%$ ) and fluvastatin (OR: 0.66, 95% CI: 0.45, 0.98,  $I^2=0.0\%$ ) had evidence to result in significantly fewer deaths due to any reason as compared to control treatment. Although statistically not significant, lovastatin resulted in numerically more deaths than control treatment (OR: 1.03, 95% CI: 0.40, 2.40,  $I^2=0.0\%$ ). Pooled estimates for atorvastatin (OR: 0.83, 95% CI: 0.65, 1.06,  $I^2=51.9\%$ ) and simvastatin (OR: 0.72, 95% CI: 0.34, 1.54,  $I^2=61.5\%$ ) were associated with considerable heterogeneity.

**Figure 5.4** – Effect of statins compared to control on all-cause mortality in the secondary prevention population).\*



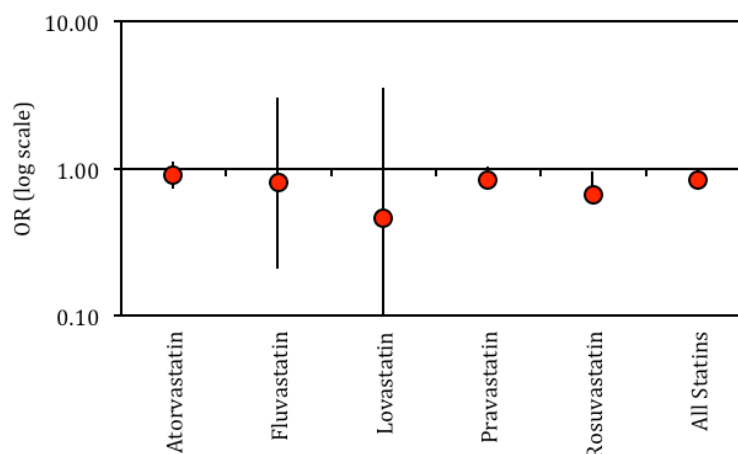
\* Estimates shown are ORs and 95% CIs. There were no trials of rosuvastatin among individuals with established coronary heart disease at baseline.

In the primary prevention population, 71,188 participants contributed information on 2,853 deaths across 18 placebo-controlled trials. There were three trials of atorvastatin providing information on 539 deaths among 13,997 individuals; one trial of fluvastatin with nine deaths among 294 individuals; two trials of lovastatin with 166 deaths among 7,690 individuals; 10 trials of pravastatin with 1,693 deaths among 29,975 individuals; and two trials of rosuvastatin with 446 deaths among 19,232 individuals. There were no trials of simvastatin.

Among individuals without prior coronary artery disease, statin therapy was associated with a significant reduction in all-cause mortality (OR: 0.91, 95% CI: 0.83, 0.99,  $I^2=8.9\%$ ) (Figure 5.5). In this population, only rosuvastatin (OR: 0.80, 95% CI: 0.66, 0.96,  $I^2=0.0\%$ ) had sufficient evidence for a significant benefit on all-cause mortality, while atorvastatin (OR: 0.91, 95% CI:

0.74, 1.12,  $I^2=23.9\%$ ), fluvastatin (OR: 0.80, 95% CI: 0.21, 3.04,  $I^2=\text{not estimated}$ ), and pravastatin (OR: 0.94, 95% CI: 0.84, 1.04,  $I^2=3.7\%$ ) did not. Lovastatin was associated with substantial heterogeneity (OR: 0.46, 95% CI: 0.06, 3.57,  $I^2=75.1\%$ ).

**Figure 5.5** – Effect of statins compared to control on all-cause mortality in the primary prevention population).\*



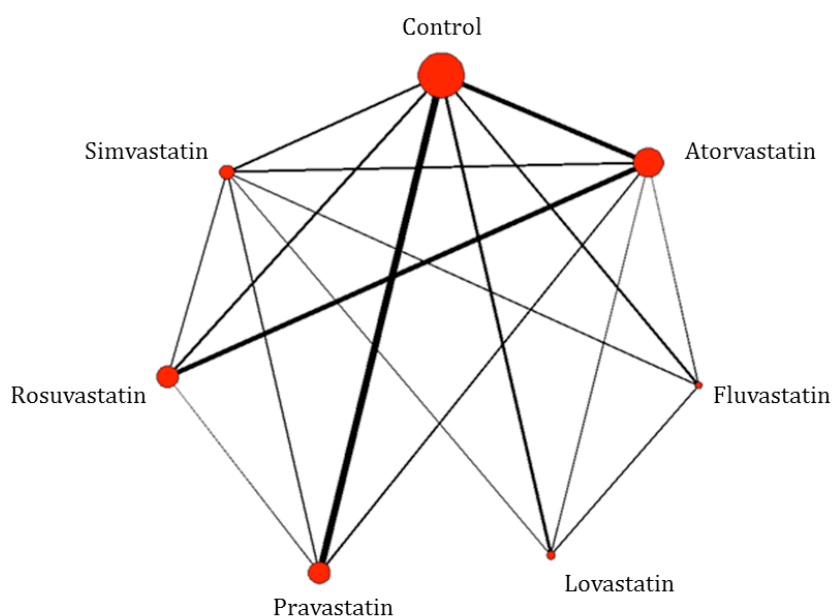
\* Estimates shown are ORs and 95% CIs. There were no trials of simvastatin among individuals with no coronary heart disease at baseline.

### 5.3.2 Comparative Benefits of Individual Statins: Findings of the Network Meta-analysis

The network of eligible comparisons is shown in Figure 5.6. In addition to the placebo-controlled trials included in the traditional pair-wise meta-analysis, a total of 41 direct comparisons including 29,643 individuals were included in the network meta-analysis of all-cause mortality. Generally, only small trials provided direct head-to-head evidence on statins in terms of all-cause mortality. As a result of the small number of events occurring in these direct head-to-head comparisons, there was large uncertainty around the results in direct comparisons. Atorvastatin was directly compared to fluvastatin in one trial including 154 individuals (OR: 0.97, 95% CI: 0.06, 15.86); to lovastatin in one trial with 156 individuals (OR: 3.04, 95% CI: 0.17, 75.75); to pravastatin in three trials involving 1,698 individuals, which demonstrated that atorvastatin was associated with significantly fewer deaths due to any reason (OR: 0.36, 95% CI: 0.15, 0.84); to rosuvastatin in 13 trials with 10,666 individuals (OR: 0.93, 95% CI: 0.44, 2.00); and to simvastatin in four trials including 12,988 individuals (OR: 0.75, 95% CI: 0.27, 2.12). Fluvastatin was compared to lovastatin in one trial with 155 individuals (OR: 3.04, 95% CI: 0.13, 73.45). Rosuvastatin was directly compared to pravastatin in two trials with

1,292 individuals (OR: 0.80, 95% CI: 0.13, 4.94); and to simvastatin in three trials with 1,678 individuals (OR: 1.60, 95% CI: 0.26, 9.83). Simvastatin was directly compared to fluvastatin in one trial with 152 individuals (OR: 2.03, 0.18, 22.86), to lovastatin in one trial with 154 individuals (OR: 0.19, 95% CI: 0.01, 4.02), and to pravastatin in one trial with 550 individuals (OR: 7.06, 95% CI: 0.36, 137.66).

**Figure 5.6** – Network of available comparisons for determining the comparative effects of individual statins on all-cause mortality.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

In the base-case network meta-analysis, 64 trials provided information for the all-cause mortality analyses. In total, 161,379 participants were included in the base-case analysis on all-cause mortality, which provided information on 11,914 deaths. The average dose was 16.7 mg/day for atorvastatin (estimated mean change from baseline LDL cholesterol as compared to control as reported in Chapter 4 [*Dose-Comparative Effects of Individual Statins on Cholesterol Concentrations*]: -48.33 mg/dL, 95% CrI: -67.89, -36.77) as compared to 40.0 mg/day for fluvastatin (-35.51 mg/dL, 95% CrI: -60.29, 0.62), 39.3 mg/day for lovastatin (-47.15 mg/dL,

95% CrI: -68.26, -20.21), 30.9 mg/day for pravastatin (-40.77 mg/dL, 95% CrI: -51.68, -27.00), 14.8 mg/day for rosuvastatin (-69.24 mg/dL, 95% CrI: -85.59, -38.81), and 33.3 mg/day for simvastatin (-54.92 mg/dL, 95% CrI: -74.13, -39.91). These dosing regimens were considered broadly similar in terms of their LDL cholesterol lowering effects with greatly overlapping 95% credible intervals.

Across all populations, there were no significant differences among statins in terms of all-cause mortality when all trials of primary prevention, secondary prevention, and mixed patient populations were pooled (Table 5.1). The statistically significant difference between atorvastatin and pravastatin was no longer obtained when all populations were pooled (OR of atorvastatin vs. pravastatin: 0.91, 95% CrI: 0.72, 1.11). Although these findings were not statistically significant, fluvastatin was associated with numerically fewer deaths due to any reason as compared to all other statins. Similarly, atorvastatin appeared to result in numerically fewer deaths than other statins, except for simvastatin, which appeared numerically and statistically equivalent (OR of atorvastatin vs. simvastatin: 0.99, 95% CrI: 0.73, 1.28).

**Table 5.1** – Comparative benefits of individual statins on all-cause mortality across all populations.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	1.11 (0.42, 2.79)	0.78 (0.52, 1.14)	0.91 (0.72, 1.11)	0.85 (0.64, 1.07)	0.99 (0.73, 1.28)
<b>Fluvastatin vs.</b>	-	0.71 (0.26, 1.87)	0.82 (0.33, 2.13)	0.76 (0.30, 2.00)	0.89 (0.34, 2.32)
<b>Lovastatin vs.</b>	-	-	1.16 (0.80, 1.68)	1.08 (0.73, 1.61)	1.26 (0.84, 1.89)
<b>Pravastatin vs.</b>	-	-	-	0.93 (0.75, 1.17)	1.08 (0.85, 1.39)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.16 (0.88, 1.53)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

As shown in Table 5.2, there were no statistically significant differences between different statins in terms of lowering the risk of all-cause mortality among individuals with established coronary heart disease at baseline. Similar to the finding across all populations, atorvastatin and fluvastatin appeared to result in numerically (but not statistically) fewer deaths due to any

reason compared to other statins. There was considerable uncertainty around the estimates of comparative benefits of individual statins.

**Table 5.2** – Comparative benefits of individual statins on all-cause mortality in the secondary prevention population.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	1.02 (0.20, 5.00)	0.93 (0.20, 4.13)	0.65 (0.24, 1.22)	0.70 (0.08, 4.18)	0.68 (0.24, 1.43)
<b>Fluvastatin vs.</b>	-	0.92 (0.13, 6.56)	0.62 (0.12, 2.62)	0.67 (0.05, 7.52)	0.66 (0.13, 2.74)
<b>Lovastatin vs.</b>	-	-	0.68 (0.16, 2.56)	0.72 (0.06, 7.99)	0.72 (0.16, 2.90)
<b>Pravastatin vs.</b>	-	-	-	1.09 (0.12, 8.42)	1.06 (0.52, 2.15)
<b>Rosuvastatin vs.</b>	-	-	-	-	0.97 (0.12, 9.24)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

Consistent with the findings in the secondary prevention population, individual statins appeared statistically equivalent to each other in terms of lowering the risk of all-cause mortality among trial participants with no prior history of coronary heart disease (Table 5.3).

**Table 5.3** – Comparative benefits of individual statins on all-cause mortality in the primary prevention population.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>
<b>Atorvastatin vs.</b>	0.99 (0.18, 5.43)	0.96 (0.45, 3.47)	0.97 (0.49, 2.17)	0.98 (0.32, 2.47)
<b>Fluvastatin vs.</b>	-	1.01 (0.19, 6.68)	1.00 (0.19, 5.21)	0.98 (0.15, 5.53)
<b>Lovastatin vs.</b>	-	-	1.01 (0.34, 2.00)	1.02 (0.22, 2.32)
<b>Pravastatin vs.</b>	-	-	-	1.02 (0.34, 2.17)

\* Estimates shown are ORs and 95% CIs. Table should be read from left to right. There were no trials of simvastatin among individuals without established coronary heart disease.

In the sensitivity analysis inclusive of high-dose trials, 80 trials provided information on a total of 13,210 deaths among 183,844 individuals. In this analysis, the average dose of atorvastatin was 39.6 mg/day as compared to 72.3 mg/day for fluvastatin, 40.7 mg/day for lovastatin, 31.2 mg/day for pravastatin, 17.2 mg/day for rosuvastatin, and 33.3 mg/day for simvastatin.

The findings of the sensitivity analysis closely paralleled the base-case network meta-analysis. There were no significant differences in the treatment benefit among statins when the trials of primary prevention, secondary prevention, and mixed patient populations were pooled for all-cause mortality (Table 5.4). Although not statistically significant, fluvastatin appeared to result in numerically fewer deaths as compared to other statins.

**Table 5.4** – Sensitivity analysis results: Comparative benefits of individual statins on all-cause mortality across all populations.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	1.22 (0.80, 1.86)	0.82 (0.57, 1.16)	0.95 (0.78, 1.13)	0.91 (0.73, 1.10)	1.01 (0.73, 1.10)
<b>Fluvastatin vs.</b>	-	0.66 (0.40, 1.13)	0.77 (0.51, 1.18)	0.74 (0.48, 1.15)	0.82 (0.53, 1.27)
<b>Lovastatin vs.</b>	-	-	1.16 (0.81, 1.65)	1.11 (0.77, 1.60)	1.23 (0.85, 1.80)
<b>Pravastatin vs.</b>	-	-	-	0.96 (0.78, 1.17)	1.06 (0.86, 1.32)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.11 (0.88, 1.40)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

Among individuals with established coronary heart disease, the sensitivity analysis results closely resembled those observed in the base-case analysis. There were no statistically significant differences between different statins although fluvastatin was again associated with numerically fewer deaths as compared to other statins (Table 5.5).

**Table 5.5** – Sensitivity analysis results: Comparative benefits of individual statins on all-cause mortality in the secondary prevention population.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	1.20 (0.72, 1.99)	0.97 (0.42, 2.25)	0.90 (0.66, 1.15)	0.49 (0.12, 1.56)	0.98 (0.68, 1.26)
<b>Fluvastatin vs.</b>	-	0.82 (0.33, 2.07)	0.75 (0.44, 1.23)	0.41 (0.09, 1.39)	0.82 (0.47, 1.37)
<b>Lovastatin vs.</b>	-	-	0.92 (0.39, 2.12)	0.51 (0.09, 1.97)	1.00 (0.42, 2.33)
<b>Pravastatin vs.</b>	-	-	-	0.55 (0.13, 1.77)	1.09 (0.77, 1.50)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.98 (0.60, 8.40)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

Including high-dose trials did not have a qualitative or statistical effect on the results for the primary prevention population. Among individuals with no history of coronary heart disease, there were no significant differences between different statins (Table 5.6).

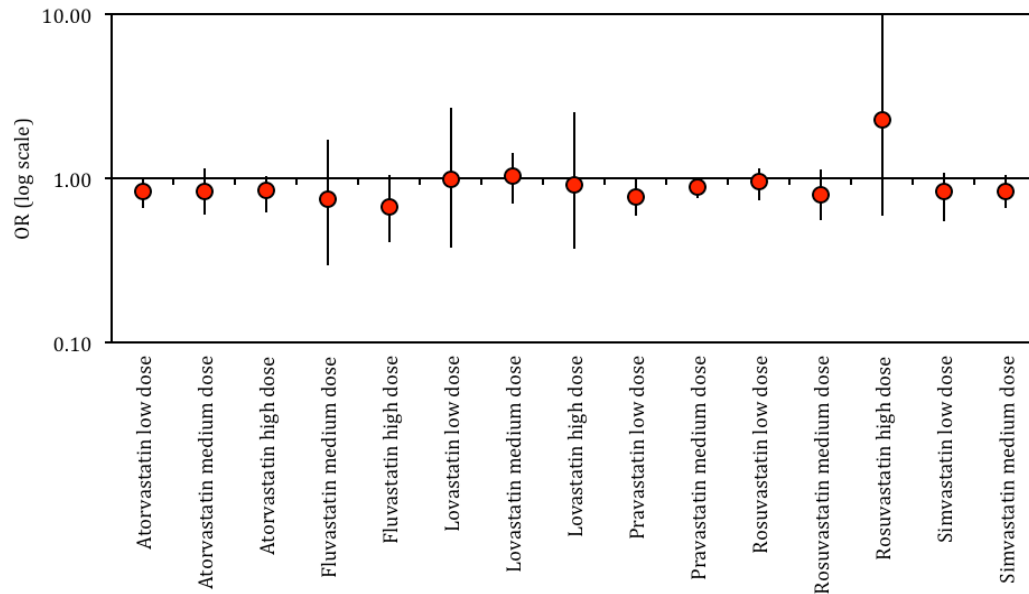
**Table 5.6** – Sensitivity analysis results: Comparative benefits of individual statins on all-cause mortality in the primary prevention population.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>
<b>Atorvastatin vs.</b>	1.13 (0.25, 5.41)	1.02 (0.59, 2.33)	1.00 (0.67, 1.60)	1.07 (0.51, 1.87)
<b>Fluvastatin vs.</b>	-	0.93 (0.19, 4.72)	0.90 (0.19, 4.01)	0.93 (0.18, 4.34)
<b>Lovastatin vs.</b>	-	-	0.98 (0.46, 1.65)	1.06 (0.35, 1.91)
<b>Pravastatin vs.</b>	-	-	-	1.08 (0.51, 1.75)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right. There were no trials of simvastatin among individuals without established coronary heart disease.

In the dose-specific analysis that included all placebo-controlled, active-comparator, and dose-comparison trials, a total of 13,892 deaths among 196,765 participants in 86 trials were included. Low-dose atorvastatin (OR: 0.83, 95% CrI: 0.66, 0.98) and low-dose pravastatin (OR: 0.77, 95% CrI: 0.59, 0.99) resulted in (marginally) significantly fewer deaths than control treatment while other statins did not have adequate evidence to show superiority over placebo (Figure 5.7). Interestingly, statins at higher doses did not have a greater impact on all-cause mortality than statins at lower doses. For instance, the all-cause mortality benefit associated with atorvastatin was consistent at low (OR: 0.83, 95% CrI: 0.66, 0.98), medium (OR: 0.84, 95% CrI: 0.60, 1.16), and high doses (OR: 0.84, 95% CrI: 0.63, 1.04). There was considerably weak evidence for rosuvastatin at high doses, which resulted in numerically more deaths as compared to control treatment; but this finding was associated with considerable uncertainty (OR: 2.28, 95% CrI: 0.59, 10.88).

**Figure 5.7 – Dose-specific analysis findings: comparative effects of individual statins compared to control for all-cause mortality across all populations.\***



\* Estimates shown are ORs and 95% CrIs.

### 5.3.3 Investigation of Heterogeneity and Inconsistency in the Network Meta-analysis

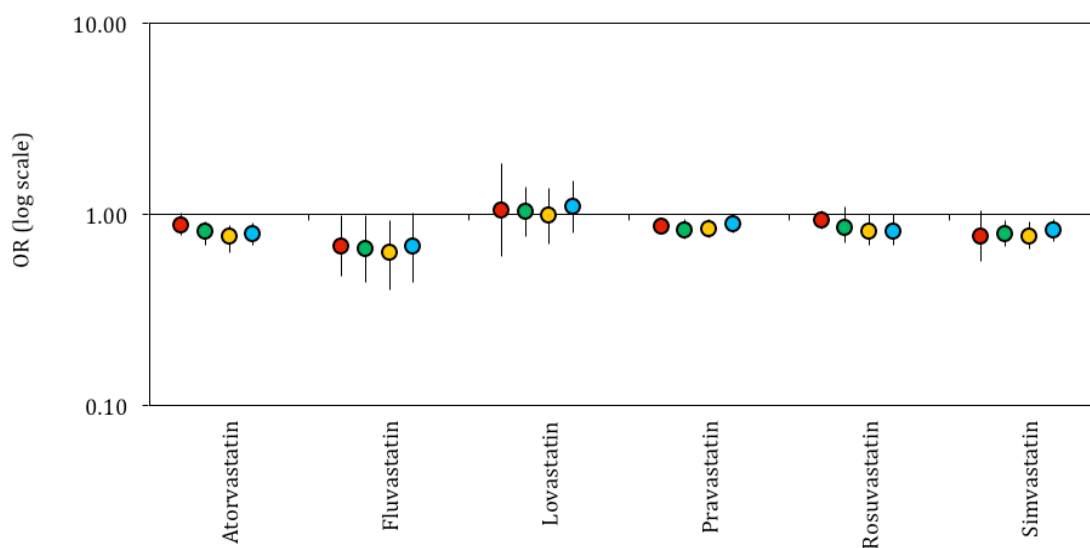
Meta-regression analyses evaluating the impact of mean age at baseline, mean LDL cholesterol concentration at baseline, and publication year could not explain the potential heterogeneity and inconsistency in the base-case network meta-analysis. Table 5.7 shows the between-study standard deviations and covariate coefficients with base-case model as compared to meta-regressions. Although the analysis that adjusted for the mean LDL cholesterol concentrations of patients at baseline showed that this covariate was marginally statistically significant, its impact on the between-study standard deviation was minimal. Figure 5.8 shows the sensitivity of relative treatment effects of statins versus control to different meta-regression analyses. According to this figure, the comparative benefits of individual statins were not sensitive to mean age at baseline, mean LDL cholesterol concentrations at baseline, and publication year: 95% credible intervals greatly overlapped between base-case and adjusted analyses. However, the observed relative treatment effect for atorvastatin and simvastatin no longer crossed the null value (1.00) when baseline mean age and LDL concentration of patients and trial publication year were taken into account in separate meta-regression analyses (Figure 5.8).

In the case of fluvastatin, adjusting for publication year resulted in a relative treatment effect, which was no longer statistically significant (OR: 0.68, 95% CrI: 0.44, 1.02).

**Table 5.7** – Findings of the meta-regression analyses for all-cause mortality.

	Between-study standard deviation	Meta-regression coefficient estimate log scale (95% CrI)
Base-case analysis	0.1258	-
Meta-regression analysis adjusting for mean age	0.1293	0.010 (-0.005, 0.024)
Meta-regression analysis adjusting for mean LDL at baseline	0.1146	-0.004 (-0.009, -0.001)
Meta-regression adjusting for publication year	0.0839	0.021 (-0.002, 0.041)

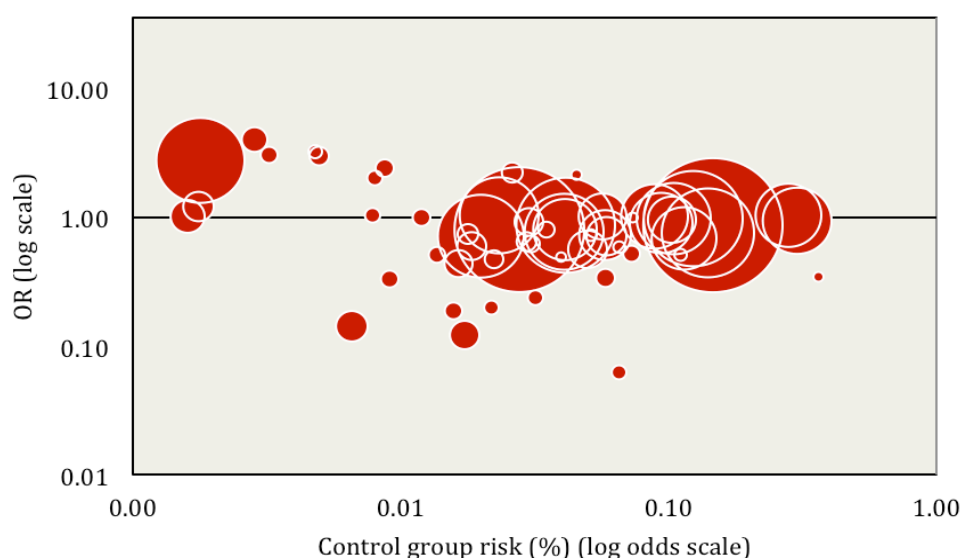
**Figure 5.8** – Sensitivity of base-case findings to meta-regression analyses for all-cause mortality.\*



\* Estimates shown are ORs and 95% CrIs. Base-case results are shown in red, while the analysis adjusted for mean age of patients at baseline is shown in green, the analysis adjusting for the mean LDL concentration at baseline is shown in yellow, and the analysis adjusting for publication year is shown in blue.

An exploration of the association between baseline risk and treatment effect in the placebo-controlled trials of statins suggested that baseline risk was not a possible explanation of between-study heterogeneity in the network meta-analyses evaluating all-cause mortality. As shown in Figure 5.9 below, there was no clear indication that baseline risk of study population modified the effect of statins on all-cause mortality in the placebo-controlled trials.

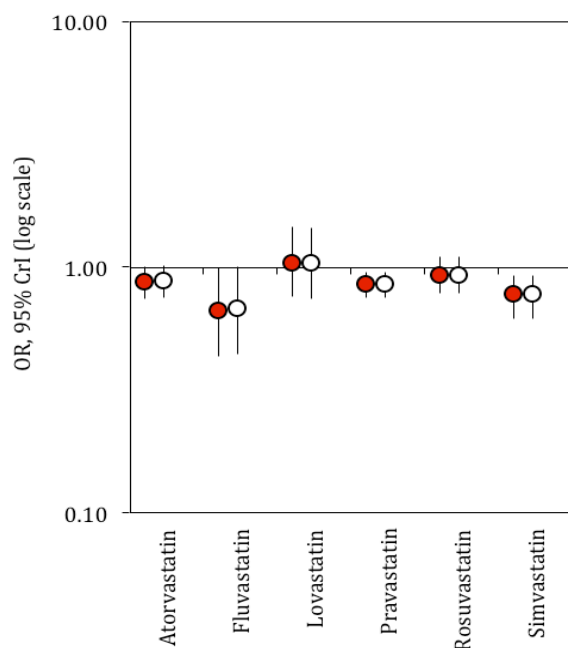
**Figure 5.9** – Relationship between the observed event rate in the control group and observed odds ratios across the placebo-controlled trials of statins. Size of the bubble is proportional to the sample size in the randomized controlled trials.



When baseline risk was considered in meta-regression analyses, it did not explain the potential heterogeneity and inconsistency in the base-case network meta-analysis for all-cause mortality. Figure 5.10 shows the sensitivity of relative treatment effects of statins versus control to the meta-regression analysis exploring the effect of baseline risk on treatment effect. According to this figure, the comparative benefits of individual statins were not sensitive to baseline risk: 95% credible intervals greatly overlapped between base-case and adjusted analyses. In addition, the meta-regression coefficient was not significant with a wide credible interval: 0.59 (95% CrI: -8.89, 9.37) and including baseline risk in the analysis did not lower the between-study heterogeneity estimate (sd in model without covariate = 0.12; sd in model with covariate = 0.12). Finally, model fit was not considerably improved when baseline risk was included as a metaregression coefficient (total residual deviance for model without covariate = 122.2; total

residual deviatnce for model with covariate = 129.7; DIC for model without covariate = 685; DIC for model with covariate = 683).

**Figure 5.10** – Sensitivity of base-case findings to meta-regression analysis exploring the effect of baseline risk on all-cause mortality.\*



\* Estimates shown are ORs and 95% CrIs. Base-case results are shown in red, while the analysis adjusted for baseline risk is shown in white.

## 5.4 Outcome 2: Major Coronary Events

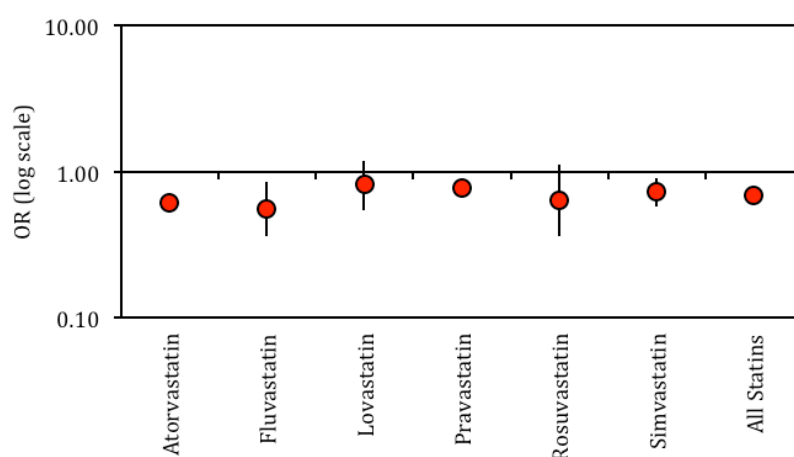
### 5.4.1 Benefits of Statins vs. Control: Findings of the Traditional Pair-wise Meta-analysis

Across all populations, 153,578 participants contributed information on 9,715 major coronary events. There were 10 trials of atorvastatin with 26,170 individuals experiencing 986 major coronary events; four trials of fluvastatin with 133 events among 3,439 individuals; eight trials of lovastatin with 446 events among 17,579 individuals; 20 trials of pravastatin with 4,032 events among 57,540 individuals; four trials of rosuvastatin with 896 events among 29,267 individuals; and five trials of simvastatin with 3,222 events among 29,297 individuals.

Overall, as shown in Figure 5.11, statin therapy was associated with a reduction in major coronary events (OR: 0.69, 95% CI: 0.64, 0.75,  $I^2=40.9\%$ ) when compared to control (see *Appendix* for trial-level results). Atorvastatin (OR: 0.61, 95% CI: 0.53, 0.70,  $I^2=0.0\%$ ), fluvastatin (OR: 0.55, 95% CI: 0.36, 0.85,  $I^2=7.4\%$ ), pravastatin (OR: 0.77, 95% CI: 0.72, 0.82,  $I^2=0.0\%$ ), and

simvastatin (OR: 0.73, 95% CI: 0.58, 0.91,  $I^2=65.3\%$ ) were associated with significantly fewer major coronary events than control treatment. Lovastatin (OR: 0.81, 95% CI: 0.55, 1.19,  $I^2=38.2\%$ ) and rosuvastatin (OR: 0.63, 95% CI: 0.36, 1.12,  $I^2=75.9\%$ ) were not associated with a reduction in major coronary events. According to contour-enhanced funnel plots, there was no evidence of differential effects between more precise and less precise trials according to contour-enhanced funnel plots (i.e., no evidence of small study effects) (see *Appendix*).

**Figure 5.11** – Effect of statins compared to control on major coronary events across all populations.\*



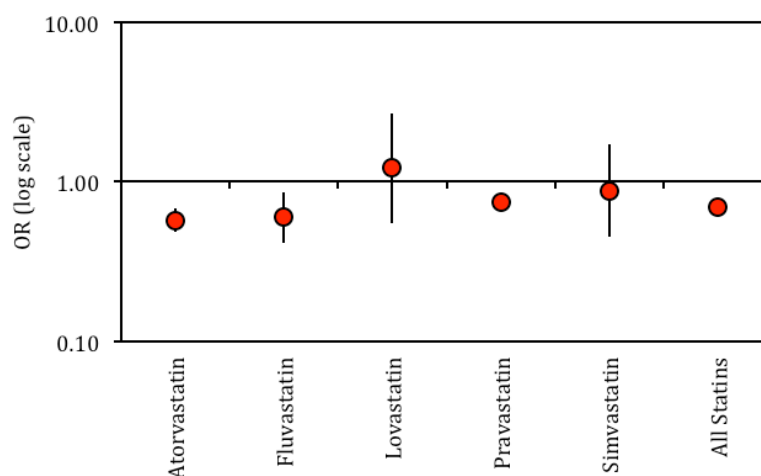
\* Estimates shown are ORs and 95% CIs.

Among individuals with established coronary artery disease, 46,585 participants contributed information on 4,265 major coronary events. There were six trials of atorvastatin with 10,218 individuals experiencing 536 major coronary events; three trials of fluvastatin with 132 events among 3,008 individuals; five trials of lovastatin with 51 events among 1,416 individuals; 11 trials of pravastatin with 2,434 events among 25,292 individuals; and four trials of simvastatin with 1,112 events among 6,651 individuals. There were no trials of rosuvastatin in this population.

In the secondary prevention population, statin therapy was associated with a significant reduction in major coronary events (OR: 0.69, 95% CI: 0.62, 0.77,  $I^2=29.4\%$ ) when compared to control (Figure 5.12). Atorvastatin (OR: 0.57, 95% CI: 0.48, 0.68,  $I^2=0.0\%$ ), fluvastatin (OR: 0.60, 95% CI: 0.41, 0.86,  $I^2=0.0\%$ ), and pravastatin (OR: 0.74, 95% CI: 0.68, 0.81,  $I^2=0.0\%$ ) led to significantly fewer major coronary events than control treatment. Lovastatin resulted in numerically more major coronary events (OR: 1.22, 95% CI: 0.55, 2.67,  $I^2=32.5\%$ ). Simvastatin

was associated with substantial heterogeneity in this population (OR: 0.87, 95% CI: 0.45, 1.70,  $I^2=70.1\%$ ).

**Figure 5.12** – Effect of statins compared to control on major coronary events in the secondary prevention population.\*

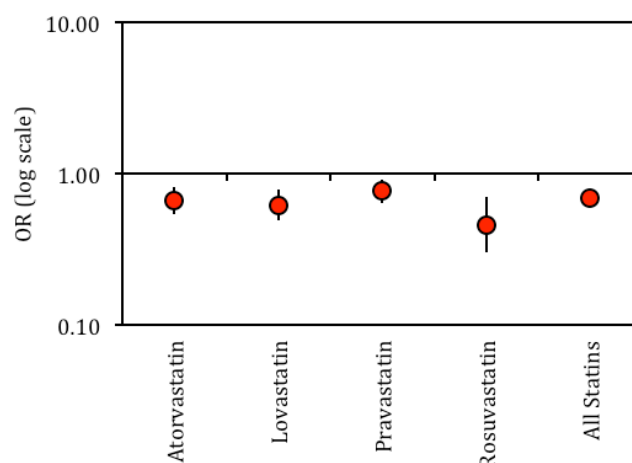


\* Estimates shown are ORs and 95% CIs. There were no trials of rosuvastatin among individuals with established coronary heart disease at baseline.

Among individuals with no prior coronary artery disease, 73,049 participants contributed information on 2,429 major coronary events. There were three trials of atorvastatin with 424 major coronary events among 15,472 individuals; two trials of lovastatin with 313 events among 7,837 individuals; 8 trials of pravastatin with 1,592 events among 30,854 individuals; and two trials of rosuvastatin with 100 events among 18,886 individuals. There were no trials of fluvastatin and simvastatin in this population.

In the primary prevention population, as shown in Figure 5.13, statin therapy was associated with a significant reduction in major coronary events (OR: 0.69, 95% CI: 0.61, 0.79,  $I^2=40.2\%$ ). Atorvastatin (OR: 0.66, 95% CI: 0.54, 0.81,  $I^2=0.0\%$ ), lovastatin (OR: 0.62, 95% CI: 0.49, 0.78,  $I^2=0.0\%$ ), pravastatin (OR: 0.77, 95% CI: 0.64, 0.91,  $I^2=37.1\%$ ), and rosuvastatin (OR: 0.46, 95% CI: 0.30, 0.70,  $I^2=0.0\%$ ) were associated with significantly fewer major coronary events as compared to control.

**Figure 5.13** – Effect of statins compared to control on major coronary events in the primary prevention population.\*

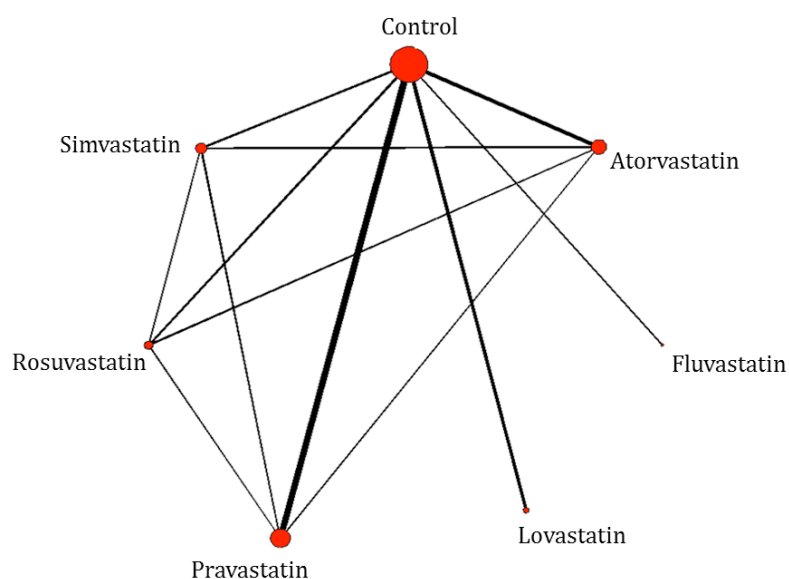


\* Estimates shown are ORs and 95% CIs. There were no trials of fluvastatin and simvastatin among individuals with no coronary heart disease at baseline.

#### 5.4.2 Comparative Benefits of Individual Statins: Findings of the Network Meta-analysis

The network of eligible comparisons for this analysis is shown in Figure 5.14. In addition to the placebo-controlled trials included in the pair-wise meta-analyses, there were 13 direct head-to-head comparisons between statins including 20,406 individuals that were not included in previous analyses. Atorvastatin was compared to pravastatin in two trials including 1,393 individuals (OR: 0.79, 95% CI: 0.46, 1.36); to rosuvastatin in four trials including 3,810 individuals (OR: 1.69, 95% CI: 0.50, 5.56); and to simvastatin in three trials including 12,831 individuals (OR: 0.87, 95% CI: 0.76, 1.01). Rosuvastatin was directly compared to pravastatin in two trials including 1,198 individuals (OR: 1.37, 95% CI: 0.14, 13.21); and to simvastatin in two trials including 1,174 individuals (OR: 1.26, 95% CI: 0.13, 12.17).

**Figure 5.14** – Network of available comparisons for determining the comparative effects of individual statins on major coronary events.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

In the base-case network meta-analysis, 48 trials provided information for the major coronary events analyses. In total, there were 9,363 events among 151,520 participants. In this analysis, the average dose was 16.7 mg/day for atorvastatin (estimated mean change from baseline LDL cholesterol as compared to control as reported in Chapter 4 [*Dose-Comparative Effects of Individual Statins on Cholesterol Concentrations*]: -48.33, 95% CrI: -67.89, -36.77) as compared to 40.0 mg/day for fluvastatin (-34.51, 95% CrI: -60.29, 0.61), 39.3 mg/day for lovastatin (-47.15, 95% CrI: -68.26, -20.21), 30.9 mg/day for pravastatin (-40.77, 95% CrI: -51.68, -27.00), 14.8 mg/day for rosuvastatin (-69.24, 95% CrI: -85.59, -38.81), and 33.3 mg/day for simvastatin (-54.92, 95% CrI: -74.13, -39.91).

When all eligible trials were pooled (overall population), there were statistically significant differences between individual statins (Table 5.8). Rosuvastatin resulted in significantly more major coronary events compared to atorvastatin (OR of atorvastatin vs. rosuvastatin: 0.66, 95% CrI: 0.48, 0.94) and fluvastatin (OR of fluvastatin vs. rosuvastatin: 0.59, 95% CrI: 0.36, 0.95). Similar to the all-cause mortality analysis findings, fluvastatin appeared to result in numerically (but not statistically) fewer major coronary events as compared to other statins.

**Table 5.8** – Comparative benefits of individual statins on major coronary events across all populations.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	1.13 (0.70, 1.85)	0.83 (0.57, 1.16)	0.82 (0.65, 1.11)	0.66 (0.48, 0.94)	0.83 (0.58, 1.10)
<b>Fluvastatin vs.</b>	-	0.74 (0.42, 1.20)	0.73 (0.48, 1.16)	0.59 (0.36, 0.95)	0.74 (0.43, 1.15)
<b>Lovastatin vs.</b>	-	-	0.99 (0.74, 1.47)	0.79 (0.56, 1.22)	1.00 (0.69, 1.38)
<b>Pravastatin vs.</b>	-	-	-	0.81 (0.58, 1.04)	1.02 (0.68, 1.24)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.27 (0.82, 1.67)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

Among participants with established cardiovascular disease, as shown in Table 5.9, atorvastatin was associated with significantly fewer major coronary events compared to pravastatin (OR: 0.65, 95% CrI: 0.43, 0.99) and simvastatin (OR: 0.68, 95% CrI: 0.38, 0.98).

**Table 5.9** – Comparative benefits of individual statins on major coronary events in the secondary prevention population.\*

	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	0.65 (0.26, 1.77)	0.65 (0.43, 0.99)	0.68 (0.38, 0.98)
<b>Lovastatin vs.</b>	-	1.01 (0.38, 2.47)	1.02 (0.36, 2.60)
<b>Pravastatin vs.</b>	-	-	1.05 (0.61, 1.39)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right. There were no trials of fluvastatin and rosuvastatin among individuals with established coronary heart disease.

As shown in Table 5.10, there were no statistical differences among individual statins without established cardiovascular disease. The findings of this analysis were associated with considerably larger uncertainty as a result of the small number of individuals included in this analysis.

**Table 5.10** – Comparative benefits of individual statins on major coronary events in the primary prevention population.\*

	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>
<b>Atorvastatin vs.</b>	1.05 (0.51, 2.27)	0.90 (0.54, 1.84)	1.41 (0.59, 3.45)
<b>Lovastatin vs.</b>	-	0.86 (0.48, 1.81)	1.35 (0.52, 3.33)
<b>Pravastatin vs.</b>	-	-	1.55 (0.63, 3.24)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right. There were no trials of fluvastatin and simvastatin among individuals without established coronary heart disease.

In the sensitivity analysis inclusive of high-dose trials, 62 trials provided information for the major coronary events analyses. There were 10,664 events among 173,062 participants. In the sensitivity analysis, the average dose of atorvastatin was 39.6 mg/day as compared to 72.3 mg/day for fluvastatin, 40.7 mg/day for lovastatin, 31.2 mg/day for pravastatin, 17.2 mg/day for rosuvastatin, and 33.3 mg/day for simvastatin.

The findings of the sensitivity analysis closely paralleled the findings of the base-case network meta-analysis. There were no significant differences in the treatment benefit among statins when the trials of primary prevention, secondary prevention, and mixed patient populations were pooled for major coronary events (Table 5.11). Although rosuvastatin was no longer statistically significantly associated with more major coronary events as compared to atorvastatin (OR: 0.75, 95% CrI: 0.57, 1.02) and fluvastatin (OR: 0.67, 95% CrI: 0.41, 1.09), it still resulted in numerically more events.

**Table 5.11** – Sensitivity analysis results: Comparative benefits of individual statins on major coronary events across all populations.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	1.11 (0.72, 1.80)	0.83 (0.58, 1.11)	0.84 (0.70, 1.05)	0.75 (0.57, 1.02)	0.84 (0.64, 1.01)
<b>Fluvastatin vs.</b>	-	0.74 (0.42, 1.20)	0.76 (0.48, 1.18)	0.67 (0.41, 1.09)	0.75 (0.44, 1.17)
<b>Lovastatin vs.</b>	-	-	1.02 (0.77, 1.48)	0.90 (0.65, 1.40)	1.01 (0.73, 1.41)
<b>Pravastatin vs.</b>	-	-	-	0.89 (0.68, 1.17)	1.00 (0.73, 1.22)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.12 (0.76, 1.47)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

However, among participants with established cardiovascular disease, atorvastatin was associated with significantly fewer major coronary events compared to lovastatin (OR: 0.47, 95% CrI: 0.27, 0.83) and pravastatin (OR: 0.77, 95% CrI: 0.64, 0.95) in the sensitivity analysis inclusive of high-dose trials (Table 5.12). Participants randomized to lovastatin were estimated to experience significantly more major coronary events than those randomized to fluvastatin (OR: 2.08, 95% CrI: 1.06, 4.17; reciprocals are reported in Table 5.12) and simvastatin (OR: 1.82, 95% CrI: 1.01, 3.22) in trials of secondary prevention.

**Table 5.12** – Sensitivity analysis results: Comparative benefits of individual statins on major coronary events in the secondary prevention population.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	0.97 (0.67, 1.52)	0.47 (0.27, 0.83)	0.77 (0.64, 0.95)	0.86 (0.67, 1.01)
<b>Fluvastatin vs.</b>	-	0.48 (0.24, 0.94)	0.79 (0.52, 1.17)	0.88 (0.54, 1.29)
<b>Lovastatin vs.</b>	-	-	1.65 (0.96, 2.90)	1.82 (1.01, 3.22)
<b>Pravastatin vs.</b>	-	-	-	1.12 (0.83, 1.34)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right. There were no trials of rosuvastatin among individuals with established coronary heart disease.

In the sensitivity analysis including high-dose trials, there were no detectable statistical differences among statins for participants without established cardiovascular disease (Table 5.13).

**Table 5.13** – Sensitivity analysis results: Comparative benefits of individual statins on major coronary events in the primary prevention population.\*

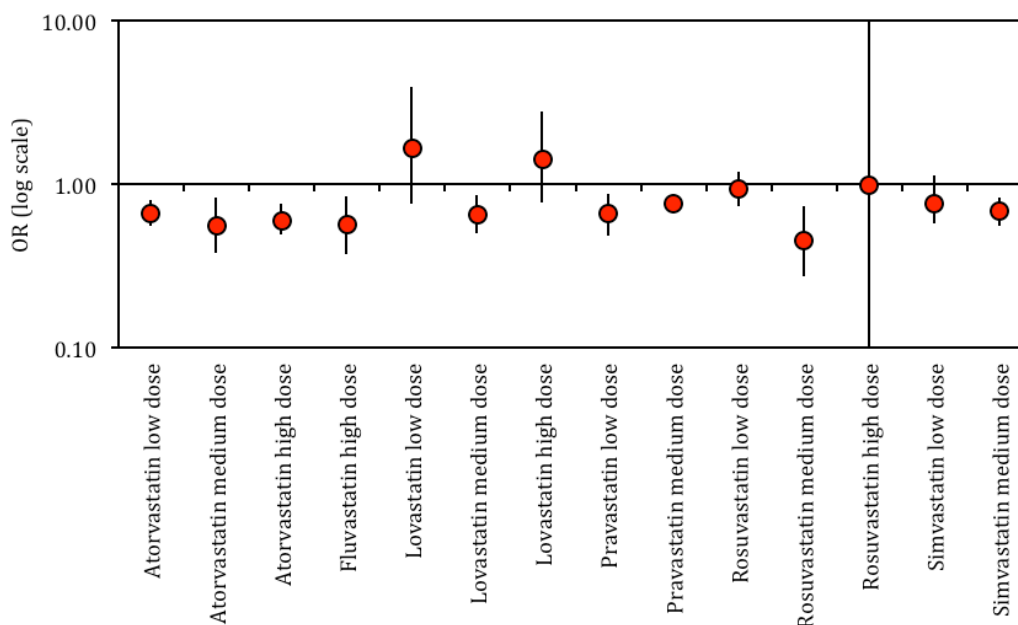
	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>
<b>Atorvastatin vs.</b>	1.10 (0.65, 1.95)	0.88 (0.63, 1.43)	1.44 (0.73, 2.83)
<b>Lovastatin vs.</b>	-	0.81 (0.51, 1.38)	1.30 (0.61, 2.70)
<b>Pravastatin vs.</b>	-	-	1.61 (0.80, 2.98)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right. There were no trials of fluvastatin and simvastatin among individuals without established coronary heart disease.

In the dose-specific analysis that included all placebo-controlled, active-comparator, and dose-comparison trials, a total of 11,515 major coronary events among 186,375 participants in 69 trials were included. Surprisingly, there was no general dose-response relationship with higher dose formulations being associated with greater coronary benefits (Figure 5.15). All statins

except for low-dose lovastatin (OR: 1.67, 95% CrI: 0.76, 3.95), high-dose lovastatin (OR: 1.42, 95% CrI: 0.77, 2.77), low-dose rosuvastatin (OR: 0.94, 95% CrI: 0.74, 1.18), high-dose rosuvastatin (OR: 0.98, 95% CrI: 0.08, 19.59), and low-dose simvastatin (OR: 0.76, 95% CrI: 0.58, 1.12) were associated with significantly fewer major coronary events as compared to control treatment. Higher doses of atorvastatin and fluvastatin had the highest number of significant differences compared with other statins.

**Figure 5.15** – Dose-specific analysis findings: comparative effects of individual statins compared to control for major coronary events across all populations.\*



\* Estimates shown are ORs and 95% CrIs.

#### 5.4.3 Investigation of Heterogeneity and Inconsistency in the Network Meta-analysis

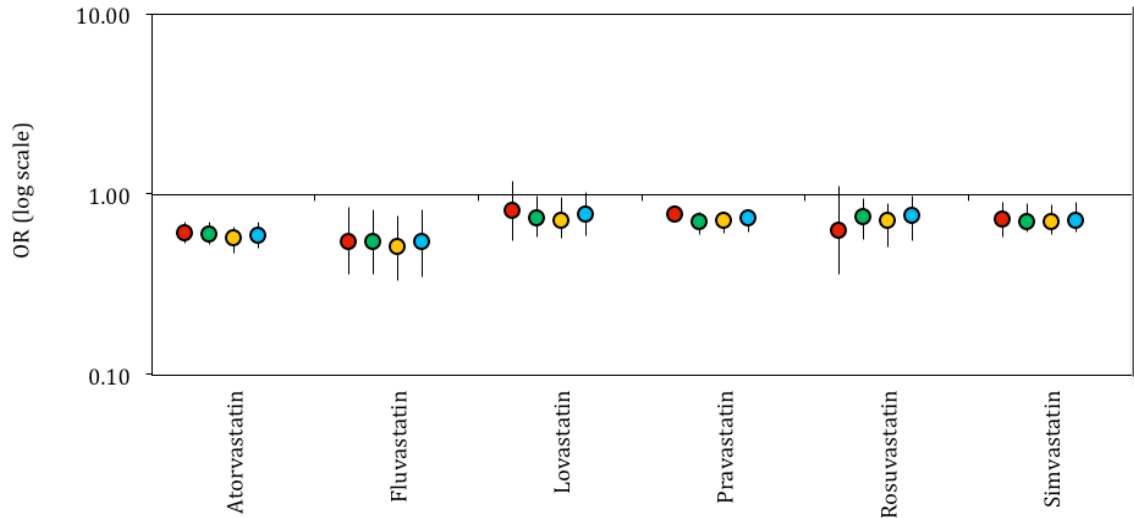
Meta-regression analyses evaluating the impact of mean age at baseline, mean LDL cholesterol concentration at baseline, and publication year could not explain the potential heterogeneity and inconsistency in the base-case network meta-analysis. Table 5.14 shows the between-study standard deviations and covariate coefficients with base-case model as compared to meta-regressions. Although the analysis that adjusted for the mean LDL cholesterol concentrations of patients at baseline showed that this covariate was marginally significant, its impact on the between-study standard deviation was minimal. Figure 5.16 shows the sensitivity of relative treatment effects of individual statins vs. control treatment to different meta-regression analyses. According to this figure, the comparative effects of individual statins on major

coronary events were not sensitive to patients' mean age at baseline, their mean LDL cholesterol concentrations at baseline, and trial publication year: 95% credible intervals greatly overlapped between base-case and meta-regression analyses for all statins. Although there was no statistically detectable difference between rosuvastatin and control treatment in the base-case network meta-analysis (OR: 0.63, 95% CrI: 0.36, 1.12), the relative treatment effect in all meta-regression analyses did not cross the null value (1.00) (Figure 5.16). In the case of lovastatin, analyses adjusting for mean age (OR: 0.74, 95% CrI: 0.58, 0.99) and LDL concentration at baseline (OR: 0.72, 95% CrI: 0.57, 0.97) resulted in narrower credible intervals around the odds ratio comparing lovastatin and control treatment.

**Table 5.14** – Findings of the meta-regression analyses for major coronary events.

	<b>Between-study standard deviation</b>	<b>Meta-regression coefficient estimate log-scale (95% CrI)</b>
Base-case	0.1479	-
Meta-regression analysis adjusting for mean age at baseline	0.1248	0.010 (-0.005, 0.025)
Meta-regression analysis adjusting for mean LDL at baseline	0.1224	-0.005 (-0.009, -0.001)
Meta-regression analysis adjusting for publication year	0.1240	0.012 (-0.015, 0.037)

**Figure 5.16** – Sensitivity of the base-case findings to meta-regression analyses for major coronary events .\*



\* Estimates shown are ORs and 95% CrIs. Base-case results are shown in red, while the analysis adjusted for mean age of patients at baseline is shown in green, the analysis adjusting for the mean LDL concentration at baseline is shown in yellow, and the analysis adjusting for publication year is shown in blue.

## 5.5 Outcome 3: Major Cerebrovascular Events

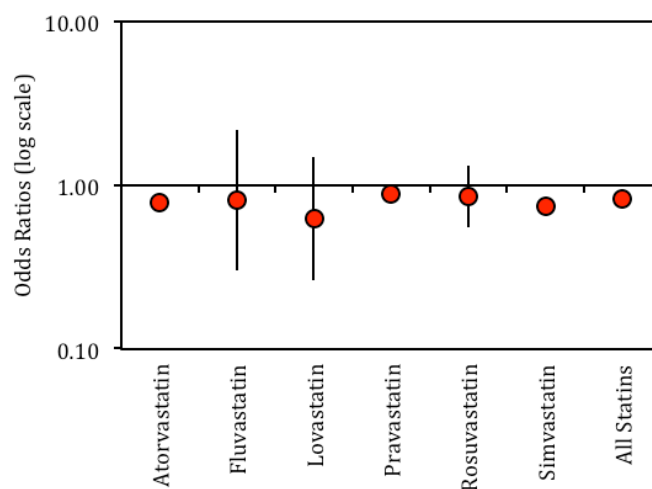
### 5.5.1 Benefits of Statins vs. Control: Findings of the Traditional Pair-wise Meta-analysis

In the traditional pair-wise meta-analysis of statin therapy vs. control across all populations, 171,731 individuals contributed information on 4,533 major cerebrovascular events (see the *Appendix* for trial-level results). There were 12 trials of atorvastatin providing information on 1,059 major cerebrovascular events among 31,739 individuals; four trials of fluvastatin with 18 events among 3,166 individuals; seven trials of lovastatin with 56 events among 17,869 individuals; 20 trials of pravastatin with 1,658 events among 63,762 individuals; three trials of rosuvastatin with 509 events among 27,896 individuals; and four trials of simvastatin with 1,233 events among 27,281 individuals.

Overall, as shown in Figure 5.17, statin therapy was associated with a reduction in the risk of major cerebrovascular events (OR: 0.82, 95% CI: 0.77, 0.87,  $I^2=0.0\%$ ) when compared to control (Figure 5.14) (see *Appendix* for trial-level results). Among statins, atorvastatin (OR: 0.78, 95% CI: 0.69, 0.89,  $I^2=0.0\%$ ), pravastatin (OR: 0.88, 95% CI: 0.80, 0.97,  $I^2=0.0\%$ ), and simvastatin (OR: 0.74, 95% CI: 0.66, 0.83,  $I^2=0.0\%$ ) were associated with a significant reduction in major

cerebrovascular events compared with the control, while fluvastatin (OR: 0.81, 95% CI: 0.30, 2.18,  $I^2=0.0\%$ ), lovastatin (OR: 0.62, 95% CI: 0.26, 1.48,  $I^2=19.5\%$ ), and rosuvastatin (OR: 0.85, 95% CI: 0.55, 1.32,  $I^2=81.3\%$ ) were not. According to contour-enhanced funnel plots, there was no evidence of differential effects between more precise and less precise trials according to contour-enhanced funnel plots (i.e., no evidence of small study effects) (see *Appendix*).

**Figure 5.17** – Effect of statins compared to control on major cerebrovascular events across all populations.\*



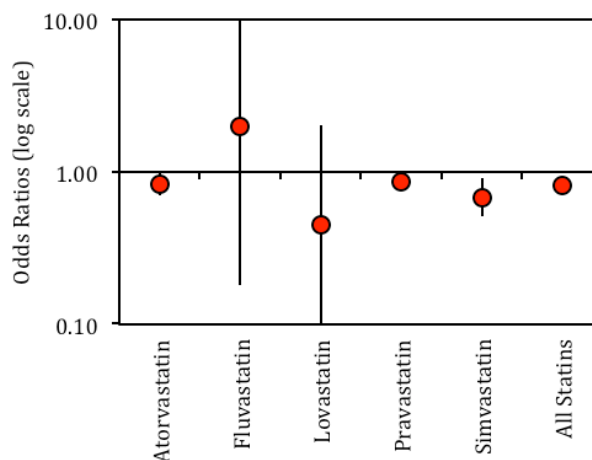
\* Estimates shown are ORs and 95% CIs.

Among individuals with established disease (secondary prevention population), 47,378 individuals contributed information on 1,748 major cerebrovascular events. There were six trials of atorvastatin providing information on 696 major cerebrovascular events among 12,283 individuals; one trial of fluvastatin with three events among 1,680 individuals; three trials of lovastatin with five events among 987 individuals; 11 trials of pravastatin with 848 events among 26,947 individuals; and three trials of simvastatin with 196 events among 5,481 individuals.

In the secondary prevention population, statin therapy was associated with a significant reduction in all-cause mortality (OR: 0.82, 95% CI: 0.75, 0.91,  $I^2=0.0\%$ ) when compared to control (Figure 5.18). Atorvastatin (OR: 0.83, 95% CI: 0.70, 0.97,  $I^2=0.0\%$ ), pravastatin (OR: 0.86, 95% CI: 0.75, 0.98,  $I^2=0.0\%$ ), and simvastatin (OR: 0.68, 95% CI: 0.51, 0.91,  $I^2=0.0\%$ ) resulted in significantly fewer events as compared to control among individuals with established history of cardiovascular disease. Pooled estimates for fluvastatin (OR: 1.98, 95% CI: 0.18, 21.84,  $I^2=\text{not}$

estimated) and lovastatin (OR: 0.45, 95% CI: 0.10, 2.03,  $I^2=0.0\%$ ) were associated with considerable uncertainty.

**Figure 5.18** – Effect of statins compared to control on major cerebrovascular events in the secondary prevention population.\*

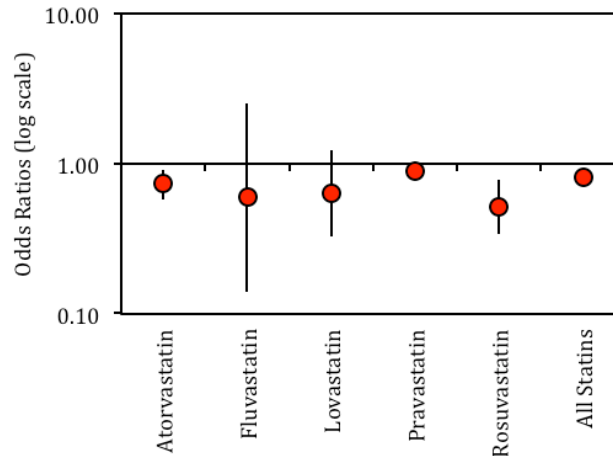


\* Estimates shown are ORs and 95% CIs. There were no trials of rosuvastatin among individuals with established coronary heart disease at baseline.

Among individuals with no prior coronary disease (primary prevention population), 72,946 individuals contributed information on 1,241 major cerebrovascular events. There were three trials of atorvastatin providing information on 322 major cerebrovascular events among 15,875 individuals; one trial of fluvastatin with eight events among 801 individuals; two trials of lovastatin with 36 events among 7,560 individuals; five trials of pravastatin with 778 events among 31,811 individuals; and one trial of rosuvastatin with 97 events among 17,899 individuals.

In the primary prevention population, statin therapy was associated with a significant reduction in major cerebrovascular events (OR: 0.81, 95% CI: 0.72, 0.90,  $I^2=9.2\%$ ) (Figure 5.19). In this population, only atorvastatin (OR: 0.73, 95% CI: 0.58, 0.91,  $I^2=0.0\%$ ) and rosuvastatin (OR: 0.51, 95% CI: 0.34, 0.78,  $I^2=\text{not estimated}$ ) had sufficient evidence for a significant benefit on major cerebrovascular events, while fluvastatin (OR: 0.60, 95% CI: 0.14, 2.53,  $I^2=\text{not estimated}$ ), lovastatin (OR: 0.64, 95% CI: 0.33, 1.24,  $I^2=55.3\%$ ), pravastatin (OR: 0.90, 95% CI: 0.78, 1.04,  $I^2=0.0\%$ ) did not. Simvastatin did not have any trials in primary prevention.

**Figure 5.19** – Effect of statins compared to control on major cerebrovascular events in the primary prevention population.\*

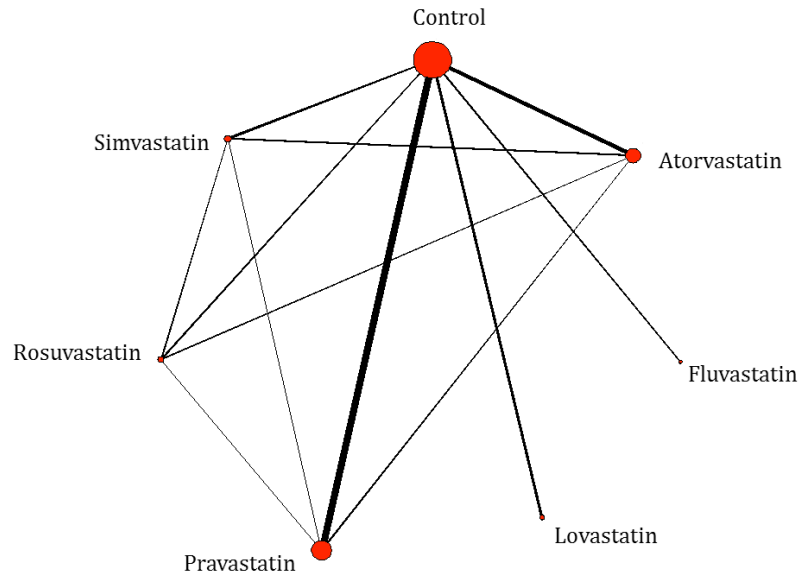


\* Estimates shown are ORs and 95% CIs. There were no trials of simvastatin among individuals with no coronary heart disease at baseline.

#### 5.5.2 Comparative Benefits of Individual Statins: Findings of the Network Meta-analysis

The network of eligible comparisons is shown in Figure 5.20. In addition to the trials included in the pair-wise comparisons of statin therapy vs. control, there were 11 direct head-to-head statin comparisons, providing information on 20,072 participants. Atorvastatin was directly compared to pravastatin in five trials including 14,973 individuals (OR: 0.88, 0.72, 1.09); to rosuvastatin in two trials including 2,400 individuals (OR: 0.66, 95% CI: 0.05, 9.42); and to simvastatin in one trial including 1,088 individuals (OR: 2.91, 95% CI: 0.12, 71.66). Rosuvastatin was directly compared to pravastatin in one trial including 367 individuals (OR: 1.78, 95% CI: 0.07, 44.11); and to simvastatin in two trials including 625 individuals (OR: 2.99, 95% CI: 0.33, 27.18).

**Figure 5.20** – Network of available comparisons for determining the comparative effects of individual statins on major cerebrovascular events.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

In the base-case network meta-analysis, 48 trials provided information for major cerebrovascular events analysis. In total, 159,554 individuals were included in the base-case analysis, which provided information on 3,916 events. In the base-case analysis, there were no significant differences between different statins in terms of major cerebrovascular events when all trials of primary prevention, secondary prevention, and mixed patient populations were pooled (overall population) (Table 5.15). Although not statistically significant, fluvastatin appeared to result in numerically fewer major cerebrovascular events as compared to other statins.

**Table 5.15** – Comparative benefits of individual statins on major cerebrovascular events across all populations.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	1.45 (0.32, 7.14)	1.07 (0.56, 1.98)	0.87 (0.64, 1.20)	0.87 (0.64, 1.20)	1.05 (0.79, 1.47)
<b>Fluvastatin vs.</b>	-	0.73 (0.13, 3.68)	0.61 (0.12, 2.73)	0.60 (0.12, 2.67)	0.74 (0.15, 3.33)
<b>Lovastatin vs.</b>	-	-	0.81 (0.46, 1.49)	0.82 (0.43, 1.55)	0.99 (0.54, 1.86)
<b>Pravastatin vs.</b>	-	-	-	1.00 (0.75, 1.30)	1.21 (0.94, 1.57)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.21 (0.88, 1.69)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

There were no statistical differences among individual statins in terms of reducing the risk of major cerebrovascular events in the secondary prevention of cardiovascular disease (Table 5.16). There was considerable uncertainty around the comparative estimate of atorvastatin vs. lovastatin (OR: 2.84, 95% CrI: 0.32, 67.75).

**Table 5.16** – Comparative benefits of individual statins on major cerebrovascular events in the secondary prevention population.\*

	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	2.84 (0.32, 67.75)**	0.94 (0.57, 1.62)	1.19 (0.65, 2.44)
<b>Lovastatin vs.</b>	-	0.33 (0.01, 2.91)	0.42 (0.02, 3.90)
<b>Pravastatin vs.</b>	-	-	1.27 (0.76, 2.27)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right. There were no trials of fluvastatin and rosuvastatin among individuals with established coronary heart disease.

\*\* There was considerable uncertainty in the relative treatment effect between atorvastatin and lovastatin due to the very small number of events.

There were also no statistically detectable differences between different statins in the primary prevention population (Table 5.17).

**Table 5.17** – Comparative benefits of individual statins on major cerebrovascular events in the primary prevention population.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>
<b>Atorvastatin vs.</b>	1.29 (0.27, 7.24)	1.21 (0.56, 2.92)	0.82 (0.57, 1.21)	1.43 (0.78, 2.65)
<b>Fluvastatin vs.</b>	-	0.93 (0.16, 5.49)	0.63 (0.12, 2.98)	1.13 (0.20, 5.66)
<b>Lovastatin vs.</b>	-	-	0.68 (0.30, 1.45)	1.18 (0.47, 2.85)
<b>Pravastatin vs.</b>	-	-	-	1.75 (0.97, 3.08)

\* Estimates shown are ORs and 95% CIs. Table should be read from left to right. There were no trials of simvastatin among individuals without established coronary heart disease.

In the sensitivity analysis including high-dose trials, 61 trials provided information for major cerebrovascular events analysis. In total, 187,038 individuals were included in the sensitivity analysis, which provided information on 4,913 events.

The findings of the base-case analysis were not sensitive to dose differentials across trials. As shown in Table 5.18, there were no statistical differences between individual statins when primary prevention, secondary prevention, and mixed patient populations were pooled together (overall population) in an analysis which included high-dose trials in addition to normal dose trials considered in the base-case analysis.

**Table 5.18** – Sensitivity analysis results: Comparative benefits of individual statins on major cerebrovascular events across all populations.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	0.94 (0.35, 2.26)	1.08 (0.60, 1.98)	0.86 (0.70, 1.04)	0.82 (0.63, 1.05)	0.99 (0.82, 1.21)
<b>Fluvastatin vs.</b>	-	1.14 (0.39, 3.82)	0.91 (0.37, 2.49)	0.86 (0.36, 2.30)	1.05 (0.43, 2.90)
<b>Lovastatin vs.</b>	-	-	0.79 (0.44, 1.44)	0.76 (0.41, 1.38)	0.91 (0.50, 1.66)
<b>Pravastatin vs.</b>	-	-	-	0.95 (0.74, 1.23)	1.15 (0.94, 1.43)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.21 (0.93, 1.62)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

Among individuals with established coronary heart disease (secondary prevention population), as shown in Table 5.19, there were no significant differences between different statins. There was substantial uncertainty around the estimate comparing atorvastatin vs. lovastatin (OR: 4.30, 95% CI: 0.61, 60.86).

**Table 5.19** – Sensitivity analysis results: Comparative benefits of individual statins on major cerebrovascular events in the secondary prevention population.\*

	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	4.30 (0.61, 60.86)	0.90 (0.64, 1.25)	0.98 (0.72, 1.40)
<b>Lovastatin vs.</b>	-	0.21 (0.01, 1.45)	0.23 (0.02, 1.63)
<b>Pravastatin vs.</b>	-	-	1.09 (0.77, 1.68)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right. There were no trials of fluvastatin and rosuvastatin among individuals with established coronary heart disease.

There were also no detectable statistical differences between individual statins in the primary prevention population (Table 5.20).

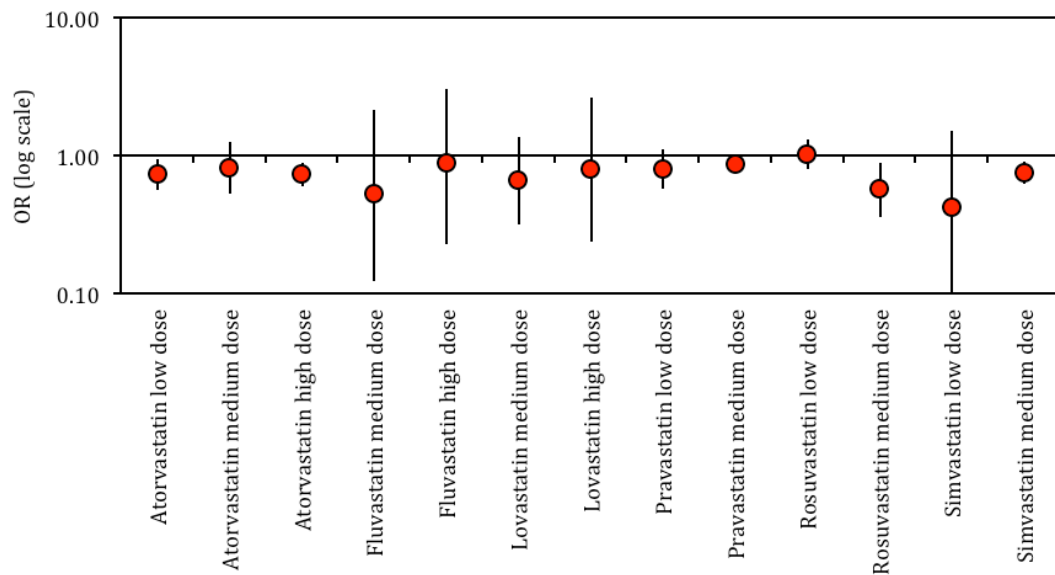
**Table 5.20** – Sensitivity analysis results: Comparative benefits of individual statins on major cerebrovascular events in the primary prevention population.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>
<b>Atorvastatin vs.</b>	1.29 (0.27, 7.24)	1.21 (0.56, 2.92)	0.82 (0.57, 1.21)	1.43 (0.78, 2.65)
<b>Fluvastatin vs.</b>	-	0.93 (0.16, 5.49)	0.63 (0.12, 2.98)	1.13 (0.20, 5.66)
<b>Lovastatin vs.</b>	-	-	0.68 (0.30, 1.45)	1.18 (0.47, 2.85)
<b>Pravastatin vs.</b>	-	-	-	1.75 (0.97, 3.08)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right. There were no trials of simvastatin among individuals without established coronary heart disease.

In the dose-specific analysis, atorvastatin low dose (OR: 0.73, 95% CrI: 0.57, 0.95), atorvastatin high dose (OR: 0.74, 95% CrI: 0.60, 0.88), rosuvastatin medium dose (OR: 0.57, 95% CrI: 0.36, 0.88), and simvastatin medium dose (OR: 0.76, 95% CrI: 0.63, 0.90) were associated with significantly fewer major cerebrovascular events as compared to control treatment (Figure 5.21).

**Figure 5.21** – Dose-specific analysis findings: comparative effects of individual statins compared to control for major coronary events across all populations.\*



\* Estimates shown are ORs and 95% CIs.

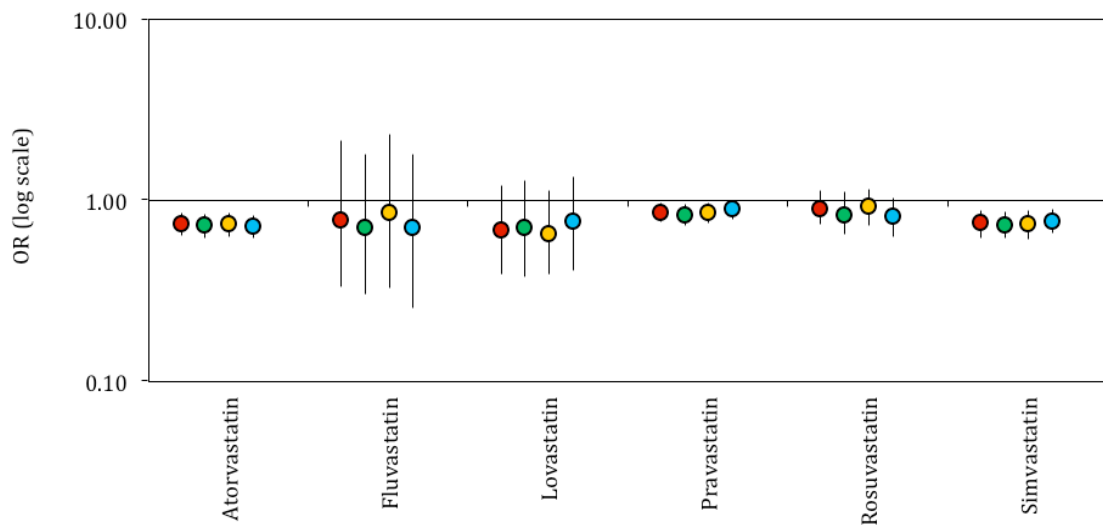
### 5.5.3 Investigation of Heterogeneity and Inconsistency in the Network Meta-analysis

Meta-regression analyses evaluating the impact of mean age at baseline, mean LDL cholesterol concentration at baseline, and publication year could not explain the potential heterogeneity and inconsistency in the base-case network meta-analysis. Table 5.21 shows the between-study standard deviations and covariate coefficients with base-case model as compared to meta-regressions. Figure 5.22 shows the sensitivity of relative treatment effects of individual statins vs. control treatment to different meta-regression analyses. According to this figure, the comparative benefits of individual statins were not sensitive to mean age at baseline, mean LDL cholesterol concentrations at baseline, and publication year.

**Table 5.21** – Findings of the meta-regression analyses for major cerebrovascular events.

	Between-study standard deviation	Meta-regression coefficient estimate log-scale (95% CrI)
Base-case	0.0945	-
Meta-regression analysis adjusting for mean age at baseline	0.0825	0.008 (-0.010, 0.024)
Meta-regression analysis adjusting for baseline LDL level	0.0945	0.000 (-0.005, 0.005)
Meta-regression analysis adjusting for publication year	0.0734	0.021, (-0.005, 0.047)

**Figure 5.22** – Sensitivity of the base-case findings to meta-regression analyses for major coronary events.\*



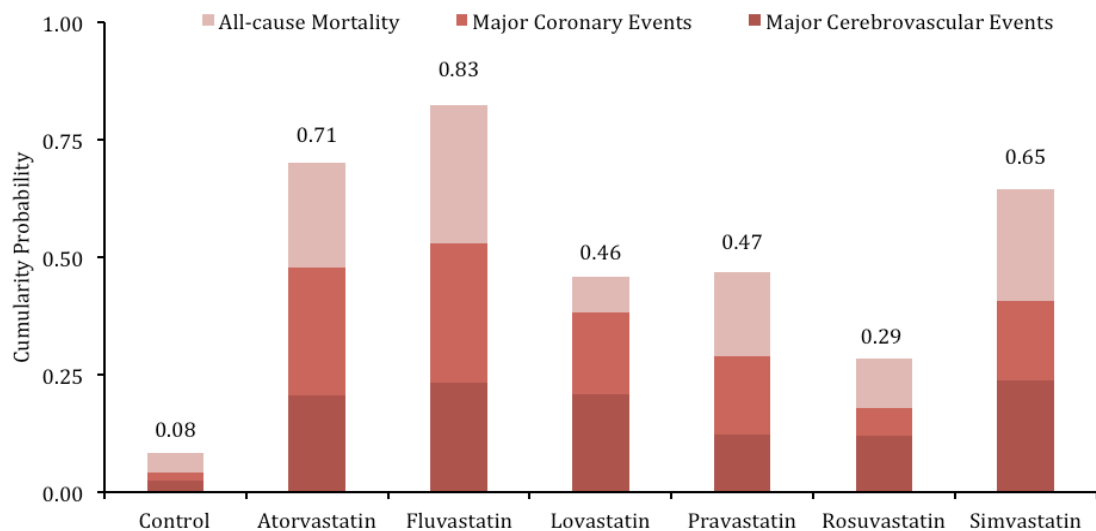
\* Estimates shown are ORs and 95% CrIs. Base-case results are shown in red, while the analysis adjusted for mean age of patients at baseline is shown in green, the analysis adjusting for the mean LDL cholesterol concentration at baseline is shown in yellow, and the analysis adjusting for publication year is shown in blue.

## 5.6 Overall Rankings of Individual Statins in terms of Benefit Outcomes Across All Populations

As outlined in the previous sections of this chapter, network meta-analyses did not detect a large number of statistical differences between individual statins in terms of their comparative effects on total mortality, major coronary events, and major cerebrovascular events. However, their effect sizes on reducing the risk of deaths and clinical endpoints across different analyses varied considerably. For instance, fluvastatin consistently resulted in the lowest OR for all-cause mortality and major coronary events.

Combining the results of the network meta-analyses on total mortality, major coronary events, and major cerebrovascular events across all populations, the overall rankings for the individual statins is shown in Figure 5.23. In addition to the overall score for each statin, the relative contribution of each outcome (mortality, coronary, and cerebrovascular events) to the overall score is also shown. Fluvastatin ranked first with an overall score of 0.83 out of 1.00, followed by atorvastatin with 0.71, and simvastatin with 0.65. As expected, control treatment ranked worst with 0.08 points out of a total of 1.00. Surprisingly, rosuvastatin, which has similar LDL cholesterol lowering effects as atorvastatin and simvastatin, ranked lower than statins with considerably lower LDL cholesterol lowering effects.

**Figure 5.23** – Ranking of individual statins on the basis of their effects on all-cause mortality, major coronary events, and major cerebrovascular events.



## 5.7 Summary of Findings

This network meta-analysis of 103 randomized trials including 214,877 individuals provided evidence on the statistically and clinically meaningful benefits of statins in both primary and secondary prevention of all-cause mortality, major coronary events, and major cerebrovascular events. Overall, statins were associated with an 18% reduction in relative odds of all-cause mortality among patients with cardiovascular disease. In primary prevention, statin therapy resulted in a modest but significant 9% reduction in relative odds of all-cause mortality. Benefits of statins in reducing the relative odds of major coronary events by 31% were consistent across primary and secondary prevention populations. Similarly, there was a consistent 18% reduction in the relative odds of major cerebrovascular events across primary prevention, secondary prevention, and overall populations. Across all populations, the base-case analysis provided evidence to suggest that individual statins are statistically equivalent in terms of their benefits on total mortality and major cerebrovascular events, but that there may be differences among individual statins for preventing major coronary events. Among individual statins, atorvastatin, fluvastatin, and simvastatin were likely to be ranked superior to their alternatives at comparable doses across all populations.

### 5.7.1 *Comparative Benefits of Statins on Total Mortality and Major Coronary Events*

The base-case network meta-analysis detected statistically significant differences among statins. Doses considered in the base-case analysis were broadly comparable and, as expected, resulted in approximately 30-40% reductions from baseline LDL cholesterol levels. Atorvastatin and fluvastatin performed significantly better than rosuvastatin in terms of reducing major coronary events across all populations. Atorvastatin and fluvastatin had a strong effect in reducing mortality and morbidity among individuals with established coronary heart disease. Among individuals with established disease, atorvastatin resulted in marginally fewer major coronary events as compared with pravastatin and simvastatin. Relative treatment effects for statins were not sensitive to the findings of the meta-regression analysis and the sensitivity analysis that included intensive dose trials. In the sensitivity analysis, atorvastatin was significantly more effective than lovastatin and pravastatin in reducing major coronary events in the secondary prevention setting. Also, fluvastatin was more effective than lovastatin in reducing major coronary events. Unfortunately, fluvastatin and simvastatin had insufficient evidence in the primary prevention setting as there was no trial for either statin that provided information for their effectiveness in high-risk individuals without established disease.

The dose-specific analysis paralleled the findings of previous meta-analyses in that statins at higher doses do not reduce all-cause mortality more so than statins at lower doses.<sup>240</sup> Similar to previous meta-analyses, there was a general dose-response relationship across placebo-controlled and active-comparator trials in terms of reducing major coronary events. However, this relationship was not apparent for all statins. For instance, low-dose and high-dose formulations of lovastatin fared worse than the medium-dose formulation.<sup>257</sup> Similarly, currently available randomized evidence is not adequate to suggest that high-dose rosuvastatin is beneficial in reducing major coronary events.<sup>349-351</sup> Although high-dose formulations of atorvastatin and fluvastatin have not been compared directly in trials, the findings of the network meta-analysis provided compelling evidence that these agents are equally effective in reducing the occurrence of major coronary events. Placebo-controlled trials of atorvastatin and fluvastatin were comparable in terms of known relative treatment effect modifiers and individuals in the placebo arms experienced major coronary events at similar rates.<sup>134,183,193,352,353</sup> Given the greatly differing incremental LDL cholesterol lowering effects of high-dose atorvastatin and fluvastatin, this analysis suggests that incremental LDL cholesterol reducing effects alone may not be responsible for the comparative benefits of statins.

### 5.7.2 *Comparative Benefits of Statins on Major Cerebrovascular Events*

The overall findings of the network meta-analysis presented in this chapter reinforce and extend the results of previous meta-analyses on statin therapy. Previous reviews elucidated the importance of lipid management with statins in the prevention of strokes and found consistent evidence that would warrant advocating statin use for the prevention of incident strokes.<sup>354,355</sup> Clinical practice guidelines also recommend statin therapy in secondary prevention of stroke for patients with non-cardioembolic stroke.<sup>356,357</sup> Since SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) was the only trial that investigated the benefits of statins for the secondary prevention of strokes in individuals with a history of transient ischemic attack or stroke, the analysis presented in this chapter did not explore the comparative benefits of statins in this population separately.<sup>358</sup> The base-case analysis in individuals with or without a history of established coronary heart disease did not detect significant differences among individual statins.

Although there were no statistical differences, this review suggested that the randomized trial evidence base for some statins was more robust and consistent than it was for others. This was particularly the case for atorvastatin and simvastatin. There was essentially no detectable heterogeneity across the trials of atorvastatin and simvastatin with consistent evidence for their

benefits in the prevention of major cerebrovascular events. Unlike simvastatin which did not have evidence in individuals with no history of coronary heart disease, atorvastatin was able to reach statistical significance in both primary and secondary prevention populations (as well as across all populations) as compared to control treatment. Trial evidence for fluvastatin and lovastatin was inconsistent across individuals with and without coronary heart disease and there was large uncertainty around the benefits of these agents in the prevention of major cerebrovascular events. Finally, there was substantial heterogeneity in the evidence base for rosuvastatin. Given the small number of trials, JUPITER appeared to drive the pooled estimates for rosuvastatin, specifically for individuals without a history of coronary heart disease.<sup>257</sup>

### 5.7.3 *Conclusions and Implications for Clinical Practice*

The primary findings of this network meta-analysis suggested that fluvastatin, which is among the least potent statins in terms of lowering LDL cholesterol concentrations, appeared to perform equally well with more potent statins such as atorvastatin and simvastatin in terms of preventing total mortality, major coronary events, and major cerebrovascular events at therapeutic doses. Indeed, in the secondary prevention setting, fluvastatin was more effective than rosuvastatin in terms of reducing the risk of major coronary events (OR: 0.59, 95% CI: 0.36 to 0.95) on the basis of the existing randomized trial evidence available in the published literature. Across all populations, fluvastatin was ranked as the best treatment option for the prevention of total mortality and clinical outcomes.

Previous reviews have shown that the cardiovascular benefits of statins are directly attributable to their LDL cholesterol lowering effects, with greater reductions in baseline LDL cholesterol levels resulting in greater risk reductions.<sup>175,239,359</sup> However, these analyses compared high dose formulations to low dose formulations without differentiating between individual statins. When dose-response relationships of individual statins are explored, as shown in this chapter, strong inferences cannot be made.

The analyses presented in this chapter have a number of relevant limitations. First, there were only a few head-to-head trials of individual statins that were prospectively designed to capture differences in clinical outcomes as primary endpoints. Second, there was an apparent asymmetry in the evidence network where specific interventions appeared to be avoided (e.g. fluvastatin), which may be indicative of a biased clinical research agenda. Third, between-study heterogeneity ranged from low to moderate across various traditional pairwise meta-analyses of statins vs. control. Hence, it remains a possibility that this analysis did not fully account for heterogeneity due to unobserved or unmeasured factors. However, random-effects models took

into account potential unexplained heterogeneity across the studies. In addition, meta-regression analyses further evaluated heterogeneity and inconsistency and did not detect a significant association between baseline risk, publication year, baseline age of patients, and baseline LDL cholesterol concentrations, and clinical outcomes.

Despite these limitations, this systematic review and meta-analysis provided strong evidence that statin therapy is effective in both the primary and secondary prevention of coronary heart disease, and that there may be differences between individual statins, which should be investigated in future prospective studies. However, prescribing decisions in clinical practice are complex and involve considerations that go beyond treatment rankings based on a selected list of long-term clinical benefit outcomes such as total mortality and clinical outcomes. In this regard, the findings of this network meta-analysis offer partial evidence to decision makers; the comparative short- and long-term harms of individual statins should also be taken into account when making prescribing decisions. The next chapter addresses this important question of comparative adverse effects associated with individual statins.

## Chapter 6

### Comparative Harms of Individual Statins\*

As shown in the previous chapter, statins are effective in the primary and secondary prevention of all-cause mortality, major coronary events, and major cerebrovascular events. The findings of the previous chapter also demonstrate that trial participants receiving fluvastatin, simvastatin, and atorvastatin appear to incur greater clinical benefit than those receiving lovastatin, pravastatin, and rosuvastatin. Based on these findings, should fluvastatin, simvastatin, and atorvastatin be prioritized given their favorable effect on important clinical outcomes? This question should be addressed in light of the potentially harmful adverse events associated with statin therapy as a drug class, and different statins individually. An evaluation of the comparative harm profiles of individual statins forms the basis of the empirical work presented in this chapter.

Statin therapy is associated with a predominantly favorable safety profile. Although rare, muscle toxicity remains the biggest concern with statin therapy.<sup>360</sup> Muscle toxicity attributable to statin therapy can range from muscle pain (termed myalgia when unaccompanied by an evidence of muscle damage) to more severe conditions, the most severe of which is a potentially fatal condition called rhabdomyolysis, which is defined as a sharp increase in serum concentrations of creatine kinase accompanied by muscle-related symptoms.<sup>361</sup> Elevations in serum concentrations of creatine kinase is a potential indication of muscle damage.<sup>362</sup> The mechanism of statin-induced muscle toxicity remains elusive but appears to be exacerbated by old age, certain co-morbidities, and the interaction of statins with other drugs.<sup>363,364</sup>

Another potential concern with statin drugs is related to their effect on liver enzymes.<sup>365</sup> Individuals receiving statins often experience asymptomatic elevations in liver enzymes, which

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\* Part of the work presented in this chapter was published with the following reference: Naci H, Brugts JJ, Ades AE. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. *Circ Cardiovasc Qual Outcomes*. 2013 Jul;6(4): 390-9.

are typically reversible and appear to be unrelated to an increased risk for hepatotoxicity.<sup>366</sup> Nonetheless, continuing statin therapy in the presence of elevated hepatic enzymes poses a therapeutic dilemma for prescribers and patients, and represents an important risk factor for treatment discontinuation.<sup>367</sup>

Statin therapy is also associated with a slightly increased risk of new-onset diabetes across all populations.<sup>368,369</sup> Although the reasons for this increase in risk are not clear, one hypothesis postulates that statins may adversely affect the glucose metabolism by impairing insulin secretion.<sup>370</sup> It is also possible that the observed risk represents a chance finding or residual confounding in randomized controlled trials of statins. Whatever the cause, statin-induced diabetes risk, which surfaced only in 2010, has resulted in a flurry of media coverage and academic debate.<sup>371-377</sup> In response, the United States Food and Drug Administration in 2012 added information on drug labels concerning an effect of statins on incident diabetes.<sup>378</sup>

Although statin therapy is increasingly common among individuals with relatively low risk for developing cardiovascular disease, there has not been any comprehensive analysis on the comparative adverse event profiles of different statins across all populations, and in sub-populations of primary and secondary prevention. At the population level, the nonrandomized observational evidence that linked statin use to increased risks of moderate or serious liver dysfunction, acute renal failure, and moderate or serious myopathy suggested that the adverse effects appeared to be similar across individual statins for each outcome except for liver dysfunction where risks were highest for fluvastatin.<sup>379</sup> In a more recent retrospective analysis of administrative data from Canada, the United Kingdom and United States, the use of high potency statins was associated with an increased rate of acute kidney injury in hospital admissions compared with low potency statins.<sup>380</sup>

A number of previous reviews of randomized controlled trials focused on statins as a class and established their favorable safety profile.<sup>381-383</sup> Large-scale meta-analyses of randomized controlled trials confirmed that the frequency of clinically significant side effects associated with statin therapy is low, concluding that “by any standard, statins are remarkably safe drugs.”<sup>384</sup> However, these previous reviews did not consider the totality of the existing randomized controlled trial evidence base: they either pooled only placebo-controlled trials or only a sub-set of active-comparator trials. In addition, previous reviews did not consider all clinically meaningful and patient-centered outcomes. Therefore, more research is needed to synthesize the evidence on a more diverse range of outcomes that are important for individuals receiving statins. These range from previously studied outcomes such as cancer<sup>385-387</sup> and diabetes<sup>368,388</sup>

to lesser studied outcomes such as muscle aches and clinically meaningful elevations in liver enzymes, which may be among factors contributing to nonadherence to long term statin therapy.<sup>389,390</sup> The impact of statins on these outcomes is needed to better inform patients and prescribers about the harms associated with statin therapy.

What is particularly lacking in the literature is evidence on the relative harms of individual statins. The existing literature provides only piecemeal information on the side effect profiles of individual statins. For example, one meta-analysis evaluated the harms of atorvastatin and concluded that the side effects observed in trial participants receiving atorvastatin were similar in frequency to those observed in individuals receiving placebo.<sup>391</sup> Another meta-analysis pooled the direct head-to-head comparisons of atorvastatin and rosuvastatin and found the adverse effect profiles of these agents to be similar at all doses.<sup>339</sup> There was also a relatively recent network meta-analysis that indirectly compared different statins to each other.<sup>392</sup> The findings of this previous network meta-analysis suggested that statins exert a similar risk across individual drugs. An important limitation of this analysis was its focus on placebo-controlled trials, which did not take into account evidence from a large number of trials with direct head-to-head comparisons of statins. Equally important, this previous network meta-analysis did not assess differences in dosages of individual statins across populations. Thus, there is a need to explore and quantify the relative tolerability and harms of different statins in the prevention of cardiovascular disease.

The objective of the empirical work presented in this chapter is to systematically review and synthesize the totality of the randomized controlled trial evidence on different statins, and determine their comparative tolerability and harms across a range of populations eligible for statin therapy. This chapter reports the findings of a comprehensive network meta-analysis that combines evidence from both placebo-controlled and active-comparator trials of statins on tolerability and harm outcomes. The overall effect of statins on these outcomes across all populations, in addition to secondary and primary prevention of coronary heart disease, is evaluated. The effects of individual statins head-to-head in these patient populations are compared, taking into account dose differences across the included set of included trials.

## **6.1 Empirical Considerations**

As described in Chapter 3 (*Evidence Review and Synthesis Methods*) separate traditional pairwise meta-analyses and network meta-analyses were performed for tolerability (number of participants who discontinued the study medication due to adverse events), elevations in hepatic transaminases (number of participants with clinically meaningful elevations in either

alanine aminotransferase, ALT, or aspartate aminotransferase, AST, three times baseline values as commonly defined by trial investigators), elevations in creatine kinase (number of participants with clinically meaningful increases in baseline creatine kinase, CK, levels as defined by trial investigators, ranging from three to 10 times higher than baseline concentrations), myalgia (number of individuals with muscle pain, as defined by trial investigators), myopathy (number of participants with 10 times baseline creatine kinase levels associated with muscle symptoms), and rhabdomyolysis (number of participants with severe muscle damage, as diagnosed by trial investigators). In addition, separate analyses were conducted on the incidence of cancer and diabetes mellitus (as defined by trial investigators).

Traditional pair-wise meta-analyses were based on placebo-controlled trials whereas the network meta-analyses combined placebo-controlled and active-comparator trials. For each endpoint, three sets of analyses were conducted. First, to obtain a comprehensive estimate of the effect of statins, all primary and secondary prevention trials were pooled in addition to trials with mixed patient populations. Subsequently, separate analyses were performed for the primary prevention and secondary prevention populations. These separate analyses were performed for the four primary outcomes, which had the most abundant data in the identified trials. These outcomes were discontinuations due to adverse events, myalgia occurrence, transaminase elevations, and creatine kinase elevations.

*Consideration of dose in the network meta-analysis:* For the base-case network meta-analysis, comparisons were performed at the drug-level, comparing individual statins to each other (e.g., atorvastatin vs. simvastatin) by pooling all available doses in the identified set of trials. A separate dose-specific analysis explored the effects of individual statins at all available doses, using a similar dose grouping as in Chapter 4 (*Dose-Comparative Effects of Individual Statins on Cholesterol Concentrations*). In this analysis, each possible statin-dose combination was treated as a different treatment and no trends were fitted or assumed. The following daily doses were considered for atorvastatin, lovastatin, pravastatin, and simvastatin:  $\leq 10$  mg,  $>10$  and  $\leq 20$  mg,  $>20$  and  $\leq 40$  mg, and  $>40$  mg. For fluvastatin, daily doses were  $\leq 20$  mg,  $>20$  and  $\leq 40$  mg, and  $>40$  mg. Given the different potency of rosuvastatin, a different dosing categorization was adopted: the daily doses for rosuvastatin were categories as  $\leq 5$  mg,  $>5$  and  $\leq 10$  mg,  $>10$  and  $\leq 20$  mg, and  $>20$  mg. All analyses were based on the total number of randomly assigned participants.

*Ranking of statins in the network meta-analysis:* The probability that each statin was the least harmful regimen was estimated by calculating the treatment effect for each statin compared with the control treatment, and counting the proportion of iterations of the Markov chain in

which each drug had the lowest treatment effect, the second lowest, and so on. Rank probabilities were separately estimated for discontinuations due to adverse events, myalgia occurrence, hepatic transaminase elevations, and creatine kinase elevations. Rankograms were developed to graphically present the distribution of ranking probabilities. Also, cumulative probability plots were developed for each outcome and the surface under the cumulative ranking line for each statin was estimated as described in Chapter 3 (*Evidence Review and Synthesis Methods*).<sup>324</sup> The surface area under the cumulative ranking line provided a numerical summary of the overall score for each statin for each outcome. Each statin was scored with points up to a maximum of 1.00, which was the weighted sum of scores separately estimated for discontinuations due to adverse events, myalgia occurrence, hepatic transaminase elevations, and creatine kinase elevations.

*Assessment of heterogeneity and inconsistency in the network meta-analysis:* Whether potential heterogeneity and inconsistency across the evidence base could be explained by differences in trial publication year, baseline LDL cholesterol concentration, and baseline mean age of patients was investigated using meta-regression analyses. All meta-regression analyses were performed by allowing for a common treatment-covariate interaction for each statin compared to control, as described in Chapter 3.<sup>327</sup> To further explore any potential inconsistency between direct and indirect evidence, the ratio of relative effects for indirect versus direct evidence was calculated.<sup>329</sup> Inconsistency was defined as the disagreement between direct and indirect evidence with a 95% CI excluding 1.00.<sup>289</sup>

*Goodness of fit:* As described previously (Chapter 3: *Evidence Review and Synthesis Methods*), the goodness of fit of the network meta-analysis models was examined using the total residual deviance (posterior mean of the deviance under a given model minus the deviance for the saturated model), and was considered to be satisfactory. In each model, the residual deviance was compared with the total number of data points in the dataset. As expected, models could not predict a zero cell since probabilities at zero or one were ruled out, which resulted in the total residual deviance estimates to appear large when there were a large number of zero cells.

*Assessment of model fit for the base-case, drug-level analysis*

	Effective number of parameters, pD	Total residual deviance	DIC
Discontinuations	155	235	825
Myalgia	76	141	647
Transaminase elevations	105	158	744
CK elevations	63	117	461

*Presentation of results:* First, the findings of the traditional pair-wise meta-analysis were presented along with estimates of heterogeneity in the pooled estimates of the identified placebo-controlled trials. Subsequently, the findings of the network meta-analysis, which combined evidence from placebo-controlled and active-comparator trials were presented. This was followed by the presentation of meta-regression results, which provided a statistical assessment of heterogeneity and inconsistency in the network meta-analysis. The results of additional exploratory inconsistency analyses were provided in the *Appendix*, along with additional detailed results that formed the basis of the main results presented in this chapter.

*Interpretation of results:* As previously, the results of the traditional pair-wise meta-analyses were reported in terms of odds ratios and 95% CIs. Given the Bayesian nature of network meta-analyses, the findings of these analyses were reported using odds ratios and 95% CrIs. In traditional pair-wise meta-analyses, the findings were considered '*statistically significant*' when the 95% confidence interval did not include the null value 1.00. Adopting the emerging convention in reporting and interpreting the findings of Bayesian network meta-analyses, 95% CrIs that did not cross the null value of 1.00 were considered 'significant'. Use of 'significance' in this way was considered consistent with the latest network meta-analyses that appeared in general medical journals.<sup>257</sup>

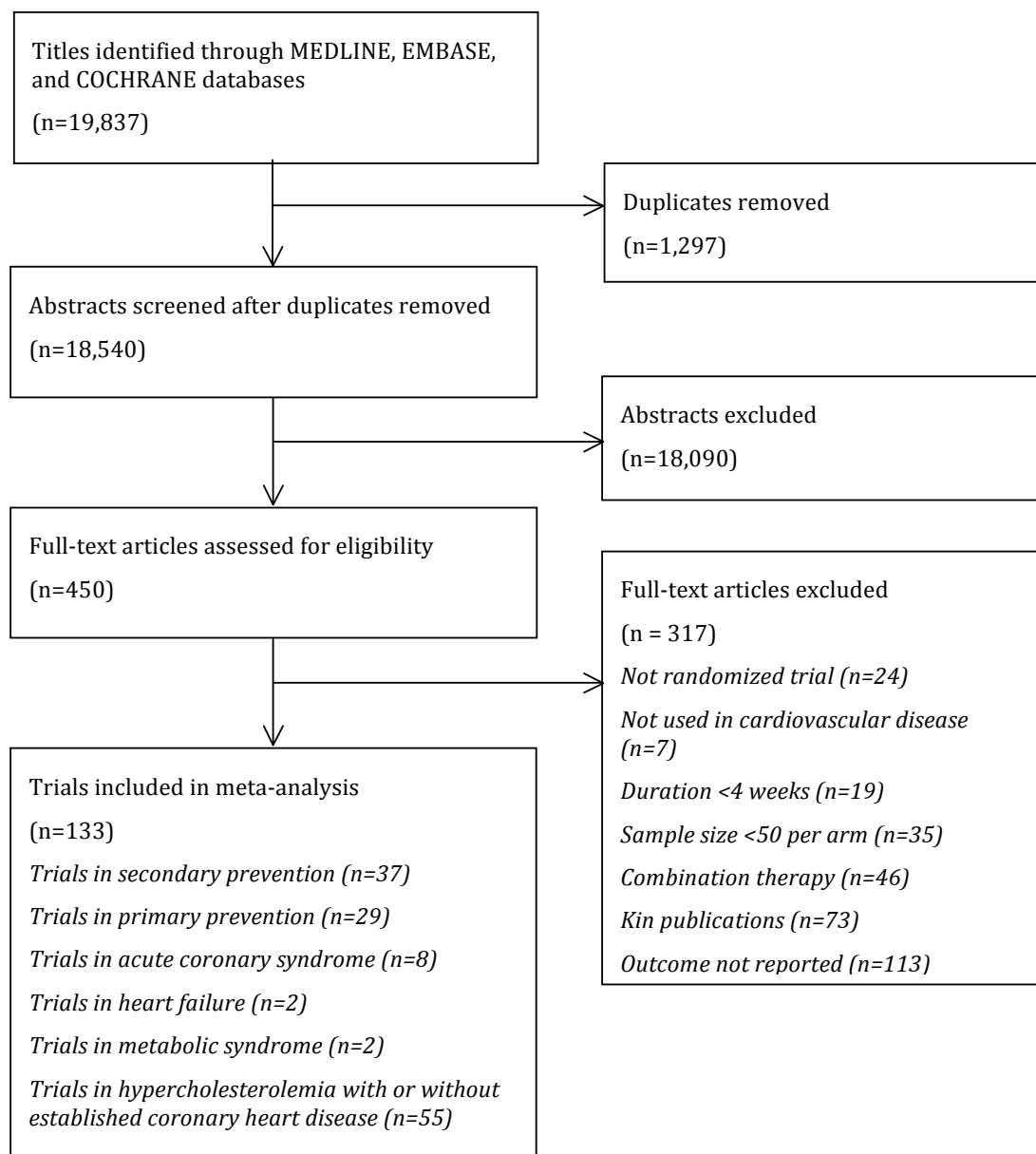
## **6.2 Systematic Review Findings**

There were 133 randomized controlled trials in the systematic review and meta-analysis of tolerability and harm outcomes (Figure 6.1). These trials included a total of 233,783 individuals. Overall, the average trial duration was 68 weeks (approximately 1.3 years). Twenty-nine trials were conducted in the primary prevention population compared with 37 trials in the secondary prevention population. The remaining 67 trials included participants with or without established cardiovascular disease. Among these, there were eight trials of patients with acute coronary syndromes, two trials that primarily included participants with heart failure, and two trials with metabolic syndrome.

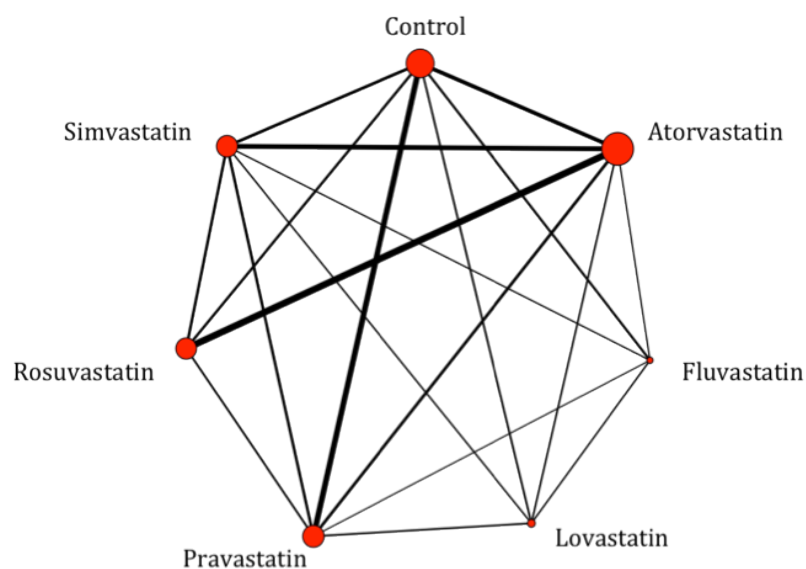
Figures 6.2 and 6.3 show the network of eligible pair-wise comparisons for tolerability and harm outcomes (discontinuations due to adverse events, myalgia occurrence, hepatic transaminase elevations, creatine kinase elevations, new-onset diabetes, cancer incidence, and rhabdomyolysis events) in placebo-controlled and active-comparator trials of individuals across all populations. Of the 15 possible pair-wise comparisons between the six statins (in the base-case analysis of drug-level comparison), 13 were available in the identified literature. The

majority of the existing pair-wise comparisons were two- or multi-arm active-comparator trials (N=78). The remaining trials were placebo-controlled trials (N=55). There were only a few trials that evaluated fluvastatin. In particular, there were only 3,500 participants randomized to fluvastatin in the eligible trials. Most frequent comparisons occurred between pravastatin and control, atorvastatin and control, and rosuvastatin and atorvastatin. A total of 52,549 participants received atorvastatin, while 35,404 participants received simvastatin, and 29,557 received pravastatin. No trial directly compared all six statins to each other for the drug-level comparison (Figure 6.2). Similarly, a small number of fluvastatin and lovastatin trials contributed to the dose-level network meta-analysis. No trial directly compared all statin-dose combinations to each other (Figure 6.3).

**Figure 6.1** - Flow diagram of trial identification and selection.

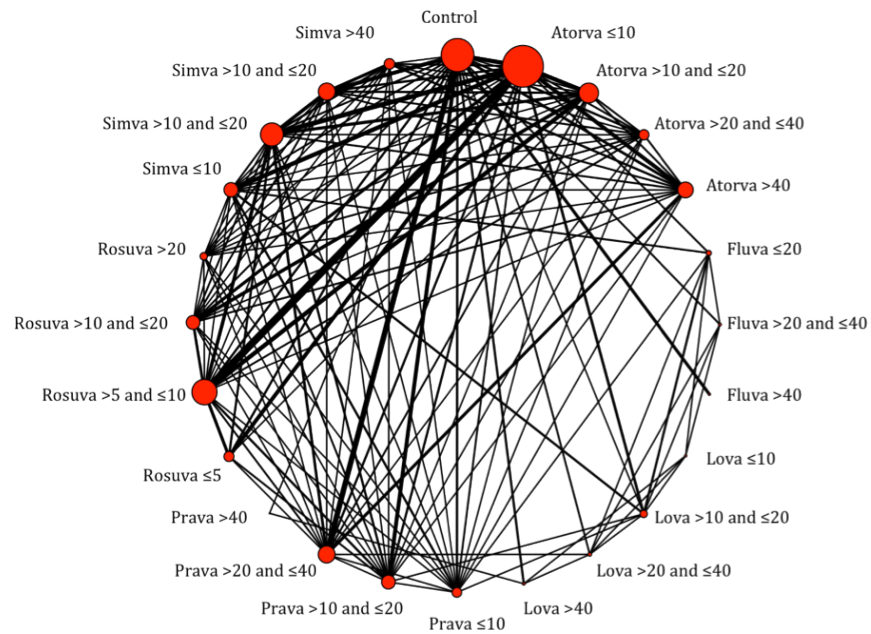


**Figure 6.2** – Network of available comparisons in the base-case drug-level network meta-analysis of tolerability and harm outcomes.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

**Figure 6.3** – Network of available comparisons in the dose-specific network meta-analysis of tolerability and harm outcomes.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

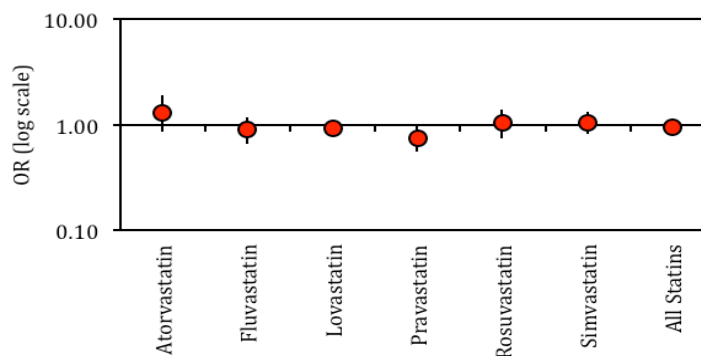
### 6.3 Outcome 1: Discontinuations due to Adverse Events

#### 6.3.1 Tolerability of Statins vs. Control: Findings of the Traditional Pair-wise Meta-analysis

In the traditional pair-wise meta-analysis of statin therapy vs. control across all populations, 76,462 participants contributed information on 5,149 discontinuations across 44 placebo-controlled trials. There were 10 trials of atorvastatin providing information on 1,302 discontinuations due to adverse events among 18,014 trial participants; five trials of fluvastatin with 492 events among 4,644 individuals; three trials of lovastatin providing information on 1,342 events among 15,097 participants; 16 trials of pravastatin with 784 events among 20,869 individuals; four trials of rosuvastatin with 890 events among 10,838 individuals; and six trials of simvastatin with 339 events among 7,000 individuals.

Overall, as shown in Figure 6.4, statin therapy was not associated with a significant increase in discontinuations due to adverse events (OR: 0.95, 95% CI: 0.83, 1.08,  $I^2=21.9\%$ ) (see *Appendix* for trial-level results). Among statins, pravastatin resulted in significantly fewer discontinuations due to adverse events (OR: 0.74, 95% CI: 0.56, 0.98,  $I^2=53.3\%$ ). Although not statistically significant, individuals receiving atorvastatin had numerically more discontinuations (OR: 1.29, 95% CI: 0.86, 1.92,  $I^2=79.4\%$ ). Fluvastatin (OR: 0.89, 95% CI: 0.67, 1.18,  $I^2=21.9\%$ ); lovastatin (OR: 0.92, 95% CI: 0.79, 1.07,  $I^2=19.7\%$ ); rosuvastatin (OR: 1.03, 95% CI: 0.75, 1.40,  $I^2=69.5\%$ ); and simvastatin (OR: 1.05, 95% CI: 0.83, 1.33,  $I^2=0.0\%$ ) were not associated with a significant increase or decrease in treatment discontinuations due to adverse events. According to contour-enhanced funnel plots, there was no evidence of small study effects (see *Appendix*).

**Figure 6.4** – Effect of statins compared to control on discontinuations due to adverse events across all populations.\*

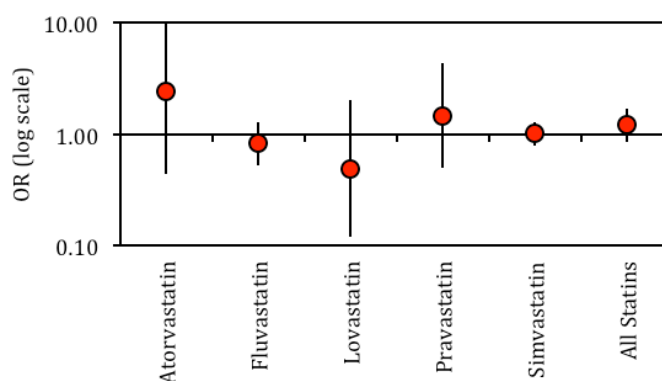


\* Estimates shown are ORs and 95% CIs.

In the secondary prevention population, 22,472 participants contributed information on 1,692 discontinuations due to adverse events across 14 placebo-controlled trials. There were four trials of atorvastatin contributing information on 848 discontinuations among 8,918 participants; three trials of fluvastatin with 404 events among 2,876 individuals; one trial of lovastatin with 9 events among 247 individuals; four trials of pravastatin with 152 events among 5,366 individuals; and two trials of simvastatin with 279 events among 5,065 individuals.

Among individuals with established coronary artery disease, statin therapy was not associated with an increase in discontinuations due to adverse events (OR: 1.20, 95% CI: 0.86, 1.68,  $I^2=78.9\%$ ) (Figure 6.5). Although not statistically significant, numerically more individuals randomized to receive atorvastatin (OR: 2.42, 95% CI: 0.44, 13.27,  $I^2=90.2\%$ ) and pravastatin (OR: 1.46, 95% CI: 0.50, 4.28,  $I^2=71.0\%$ ) discontinued treatment due to adverse events as compared to those randomized to receive control (these analyses had considerable heterogeneity). There were no significant differences between trial participants receiving lovastatin (OR: 0.49, 95% CI: 0.12, 2.01,  $I^2=0.0\%$ ) and simvastatin (OR: 1.01, 95% CI: 0.79, 1.28,  $I^2=0.0\%$ ) as compared to those receiving control.

**Figure 6.5** – Effect of statins compared to control on discontinuations due to adverse events in the secondary prevention population.\*



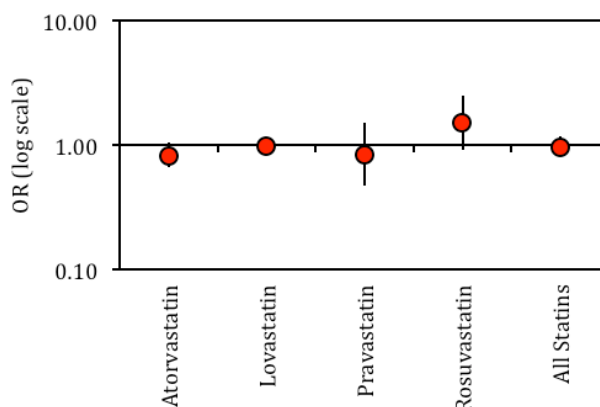
\* Estimates shown are ORs and 95% CIs.

In the primary prevention population, 20,864 trial participants contributed information on 1,623 discontinuations due to adverse events across 10 trials (see *Appendix* for trial-level results). There were two trials of atorvastatin providing information on 338 discontinuation events among 5,248 trial participants; one trial of lovastatin with 904 events among 6,605

individuals; six trials of pravastatin with 280 events among 8,027 individuals; and one trial of rosuvastatin with 101 events among 984 individuals.

Among individuals without prior coronary artery disease, statin therapy was not associated with a significant increase in discontinuations due to adverse events (OR: 0.96, 95% CI: 0.80, 1.15,  $I^2=36.4\%$ ) (Figure 6.6). Numerically more discontinuations occurred among trial participants randomized to receive rosuvastatin (OR: 1.50, 95% CI: 0.91, 2.46,  $I^2=0.0\%$ ) as compared to those receiving control. In this population, neither atorvastatin (OR: 0.82, 95% CI: 0.66, 1.03,  $I^2=0.0\%$ ) nor lovastatin (OR: 0.98, 95% CI: 0.85, 1.13,  $I^2=0.0\%$ ) differed from control in terms of their effect on treatment discontinuations due to adverse events.

**Figure 6.6** – Effect of statins compared to control on all-cause mortality in the primary prevention population.\*



\* Estimates shown are ORs and 95% CIs.

### 6.3.2 Comparative Tolerability of Individual Statins: Findings of the Network Meta-analysis

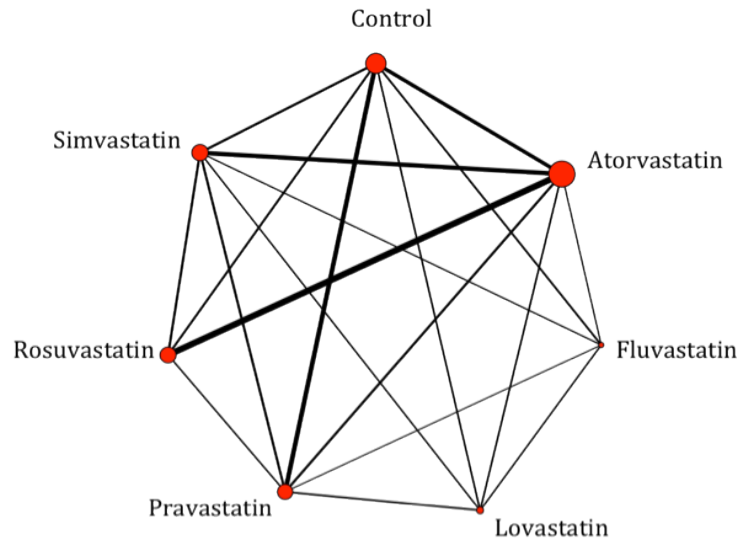
The network of eligible comparisons is shown in Figure 6.7. In addition to the placebo-controlled trials included in the traditional pair-wise meta-analysis, a total of 84 direct comparisons including 73,030 individuals were included in the network meta-analysis of discontinuations due to adverse events.†††

Atorvastatin was directly compared to fluvastatin in two trials including 1,733 individuals (OR: 0.85, 95% CI: 0.62, 1.16,  $I^2=0.0\%$ ); to lovastatin in four trials including 3,347 individuals (OR: 0.77, 95% CI: 0.55, 1.07,  $I^2=0.0\%$ ); to pravastatin in seven trials including 6,126 individuals,

††† The number of trial participants outlined in the following section does not add up to this total due to double counting of multi-arm trials that included two or more active comparators.

which showed that individuals randomized to atorvastatin were more likely to discontinue treatment due to adverse events (OR: 1.41, 95% CI: 1.07, 1.82,  $I^2=14.4\%$ ); to rosuvastatin in 25 trials including 17,615 individuals (OR: 0.96, 0.79, 1.16,  $I^2=17.1\%$ ); and to simvastatin in 16 trials including 25,501 individuals, which demonstrated that atorvastatin was marginally less tolerable than simvastatin (OR: 1.37, 95% CI: 1.00, 1.89,  $I^2=75.3\%$ ). Fluvastatin was compared to lovastatin in three trials including 1,945 individuals (OR: 1.61, 95% CI: 1.15, 2.27,  $I^2=0.0\%$ ); to pravastatin in one trial including 939 individuals, which indicated that fluvastatin was associated with significantly more discontinuations due to adverse events (OR: 3.42, 95% CI: 2.04, 5.76,  $I^2=0.0\%$ ); and to simvastatin in two trials including 1,097 individuals, which demonstrated that fluvastatin was less tolerable than simvastatin (OR: 1.72, 95% CI: 1.14, 2.56,  $I^2=0.0\%$ ). Lovastatin was directly compared to pravastatin in four trials including 2,197 individuals, showing that lovastatin resulted in more discontinuations due to adverse events as compared to pravastatin (OR: 1.69, 95% CI: 1.08, 2.63,  $I^2=0.0\%$ ); and to simvastatin in three trials including 1,256 individuals (OR: 1.07, 95% CI: 0.69, 1.66,  $I^2=0.0\%$ ). There were three trials directly comparing pravastatin to rosuvastatin, which included 1,695 individuals (OR: 1.00, 0.58, 1.69,  $I^2=0.0\%$ ); and seven trials directly comparing pravastatin to simvastatin, which included 3,676 individuals (OR: 0.76, 0.53, 1.08,  $I^2=0.0\%$ ). Rosuvastatin was directly compared to simvastatin in seven trials including 5,903 individuals (OR: 1.23, 95% CI: 0.83, 1.82,  $I^2=34.1\%$ ).

**Figure 6.7** – Network of available comparisons for determining the comparative effects of individual statins on discontinuations due to adverse events.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

In the base-case network meta-analysis, 96 trials provided information for the discontinuations due to adverse events analyses. In total, 128,842 participants contributed information on 7,626 events (6% of all participants). Across all populations, there were no significant differences among statins in terms of discontinuations due to adverse events when all trials of primary prevention, secondary prevention, and mixed patient populations were pooled (Table 6.1).

**Table 6.1** – Comparative tolerability of individual statins in terms of discontinuations due to adverse events across all populations.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	0.95 (0.63, 1.45)	1.24 (0.84, 1.87)	1.46 (1.11, 1.92)	1.01 (0.82, 1.25)	1.32 (1.05, 1.68)
<b>Fluvastatin vs.</b>	-	1.30 (0.81, 2.10)	1.53 (0.98, 2.34)	1.06 (0.68, 1.63)	1.39 (0.88, 2.14)
<b>Lovastatin vs.</b>	-	-	1.17 (0.77, 1.78)	0.81 (0.53, 1.25)	1.06 (0.69, 1.63)
<b>Pravastatin vs.</b>	-	-	-	0.69 (0.51, 0.94)	0.91 (0.67, 1.24)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.31 (1.00, 1.73)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

Individuals randomized to atorvastatin were significantly more likely to stop statin treatment due to adverse events as compared to those randomized to pravastatin (OR: 1.46, 95% CrI: 1.11, 1.92) and simvastatin (OR: 1.32, 95% CrI: 1.05, 1.68) (Table 6.1). In a similar fashion, the odds of discontinuing therapy because of adverse events were significantly higher for individuals receiving rosuvastatin as compared to those receiving pravastatin (OR: 0.69, 95% CrI: 0.51, 0.94). The statistically significant difference between fluvastatin and pravastatin observed in the traditional pair-wise meta-analysis was no longer obtained when all populations were pooled in network meta-analyses (OR of fluvastatin vs. pravastatin: 1.53, 95% CrI: 0.98, 2.34). Fluvastatin was consistently associated with numerically more discontinuations due to adverse events. There was a marginal statistical difference between rosuvastatin and simvastatin (OR of rosuvastatin vs. simvastatin: 1.31, 95% CrI: 1.00, 1.73).

As shown in Table 6.2, there were no statistically significant differences between different statins in terms of tolerability outcomes among individuals with established coronary heart disease at baseline. Although atorvastatin was still associated with numerically more discontinuations as compared to other statins, it was no longer significantly associated with more discontinuations due to adverse events due to wider 95% credibility intervals observed in this population. In general, there was considerable uncertainty around the estimates of comparative tolerability of individual statins.

**Table 6.2** – Comparative tolerability of individual statins in terms of discontinuations due to adverse events in the secondary prevention population.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	2.06 (0.75, 5.57)	3.26 (0.71, 15.92)	1.12 (0.46, 2.38)	1.06 (0.58, 1.98)	1.68 (0.84, 3.41)
<b>Fluvastatin vs.</b>	-	1.59 (0.32, 8.51)	0.54 (0.17, 1.59)	0.52 (0.16, 1.69)	0.82 (0.28, 2.40)
<b>Lovastatin vs.</b>	-	-	0.34 (0.06, 1.69)	0.33 (0.06, 1.72)	0.52 (0.1, 2.42)
<b>Pravastatin vs.</b>	-	-	-	0.95 (0.36, 2.85)	1.50 (0.6, 4.39)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.58 (0.62, 4.01)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

Consistent with the findings in the secondary prevention population, individual statins appeared statistically equivalent to each other in terms of their effects on treatment discontinuations due to adverse events among trial participants with no prior history of coronary heart disease (Table 6.3).

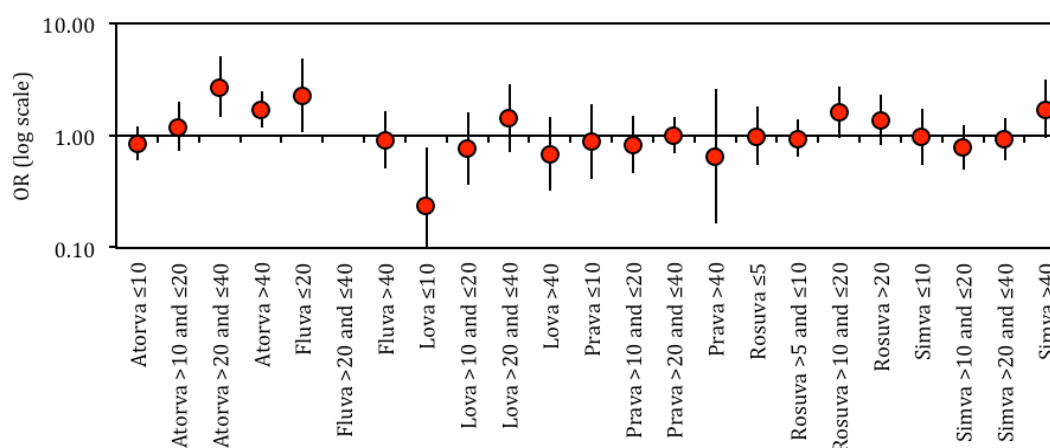
**Table 6.3** – Comparative tolerability of individual statins in terms of discontinuations due to adverse events in the primary prevention population.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	1.28 (0.54, 3.23)	1.34 (0.71, 2.43)	1.02 (0.60, 1.71)	1.05 (0.44, 2.65)	1.1 (0.41, 3.04)
<b>Fluvastatin vs.</b>	-	1.05 (0.42, 2.32)	0.79 (0.29, 2.01)	0.82 (0.25, 2.68)	0.86 (0.23, 3.07)
<b>Lovastatin vs.</b>	-	-	0.76 (0.38, 1.57)	0.78 (0.32, 2.15)	0.82 (0.28, 2.59)
<b>Pravastatin vs.</b>	-	-	-	1.04 (0.43, 2.71)	1.09 (0.40, 3.04)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.05 (0.35, 3.07)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

In the dose-specific analysis that included all placebo-controlled, active-comparator, and dose-comparison trials, a total of 8,523 discontinuations due to adverse events among 148,566 participants in 111 trials were included. Atorvastatin at >20 and ≤40 mg/day (OR: 2.50, 95% CrI: 1.48, 4.32) and at >40 mg/day (OR: 1.66, 95% CrI: 1.17, 2.38) led to significantly more discontinuations as compared to control. Similarly, individuals receiving fluvastatin at >20 and ≤40 mg/day were more likely to discontinue treatment as compared to control as a result of experiencing adverse events (OR: 2.26, 95% CrI: 1.07, 4.90). Conversely, lovastatin at ≤10 mg/day led to fewer discontinuations due to adverse events as compared to control treatment (OR: 0.24, 95% CrI: 0.07, 0.77). Although atorvastatin and simvastatin appeared to have a dose-response relationship, surprisingly, there was not a strong dose-response relationship for most statin-dose combinations (higher doses did not necessarily result in higher discontinuation rates) (Figure 6.8).

**Figure 6.8** – Dose-specific analysis findings: Comparative effects of individual statins compared to control for discontinuations due to adverse events across all populations.\*



\* Estimates shown are ORs and 95% CrIs. There were no trials of fluvastatin at >20 and ≤40 mg/day among individuals with and without prior coronary heart disease (overall population).

### 6.3.3 Investigation of Heterogeneity and Inconsistency in the Network Meta-analysis

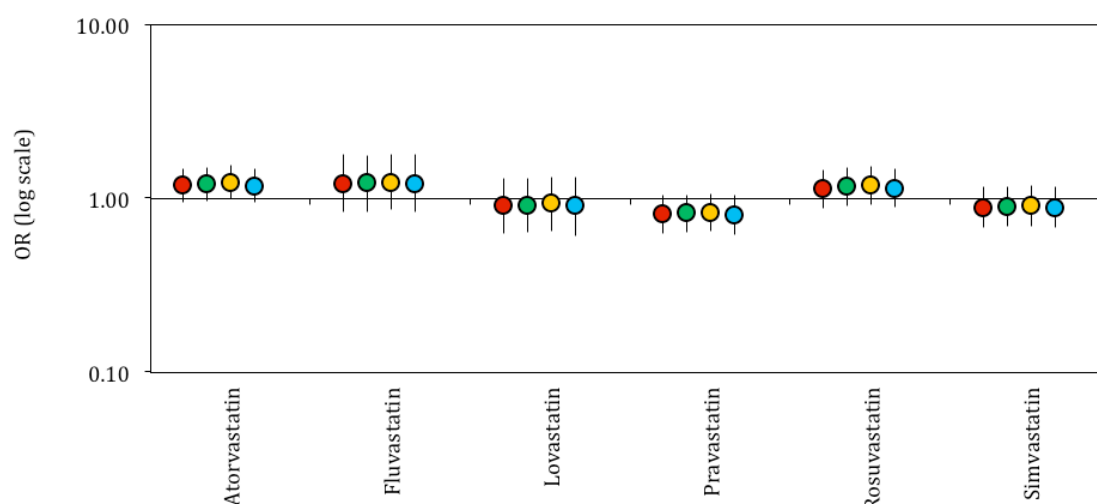
Meta-regression analyses evaluating the impact of mean age at baseline, mean LDL-C concentration at baseline, and publication year could not explain the potential heterogeneity and inconsistency in the base-case network meta-analysis. Table 6.4 shows the between-study standard deviations and covariate coefficients with base-case model as compared to meta-regressions. Figure 6.9 shows the sensitivity of relative treatment effects of statins vs. control to

different meta-regression analyses. According to this figure, the comparative effects of individual statins on discontinuations due to adverse events were not sensitive to mean age at baseline, mean LDL cholesterol concentrations, and publication year. Neither the magnitude of the relative treatment effects nor their uncertainty changed materially in various meta-regression analyses. There was no statistically detectable inconsistency between direct and indirect evidence (see *Appendix*).

**Table 6.4** – Findings of the meta-regression analyses for discontinuations due to adverse events.

	<b>Between-study heterogeneity (standard deviation)</b>	<b>Meta-regression coefficient estimate, log scale (95% CrI)</b>
Base-case analysis	0.4260	-
Meta-regression analysis adjusting for mean age of patients	0.4197	-0.02 (-0.06, 0.01)
Meta-regression analysis adjusting for LDL cholesterol at baseline	0.4126	0.01 (0.00, 0.02)
Meta-regression analysis adjusting for publication year	0.4256	0.00 (-0.06, 0.05)

**Figure 6.9** – Sensitivity of the base-case findings to meta-regression analyses for discontinuations due to adverse events.\*



\* Estimates shown are ORs and 95% CrIs. Base-case results are shown in red, while the analysis adjusted for mean age of patients at baseline is shown in green, the analysis adjusting for the mean LDL concentration at baseline is shown in yellow, and the analysis adjusting for publication year is shown in blue.

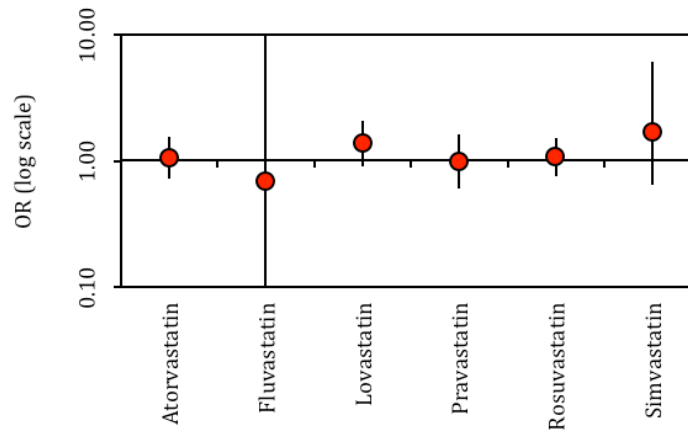
## 6.4 Outcome 2: Myalgia

### 6.4.1 Harms of Statins vs. Control: Findings of the Traditional Pair-wise Meta-analysis

Across all populations, 43,531 participants contributed information on 952 myalgia events. There were three trials of atorvastatin with 9,979 individuals experiencing 458 events; two trials of fluvastatin with 14 events among 2,063 individuals; two trials of lovastatin with 177 events among 8,492 individuals; six trials of pravastatin with 123 events among 16,428 individuals; two trials of rosuvastatin with 167 events among 5,558 individuals; and two trials of simvastatin including 1,011 individuals experiencing 13 myalgia events.

Overall, as shown in Figure 6.10, statin therapy as a class was not associated with an increase in the risk of myalgia occurrence (OR: 1.07, 95% CI: 0.89, 1.29,  $I^2$ : 22.1%) (see the *Appendix* for trial-level results). According to pair-wise meta-analyses, atorvastatin (OR: 1.05, 95% CI: 0.72, 1.54,  $I^2$ =69.5%); fluvastatin (OR: 0.69, 95% CI: 0.03, 14.83,  $I^2$ =73.3%); lovastatin (OR: 1.37, 95% CI: 0.91, 2.05,  $I^2$ =0.0%); pravastatin (OR: 0.99, 95% CI: 0.60, 1.62,  $I^2$ =19.2%); rosuvastatin (OR: 1.07, 95% CI: 0.76, 1.51,  $I^2$ =0.0%); and simvastatin (OR: 1.67, 95% CI: 0.45, 6.11,  $I^2$ =0.0%) were not associated with incident myalgia events. According to contour-enhanced funnel plots, there was no evidence of small study effects (see *Appendix*).

**Figure 6.10** – Effect of statins compared to control on incident myalgia across all populations.\*

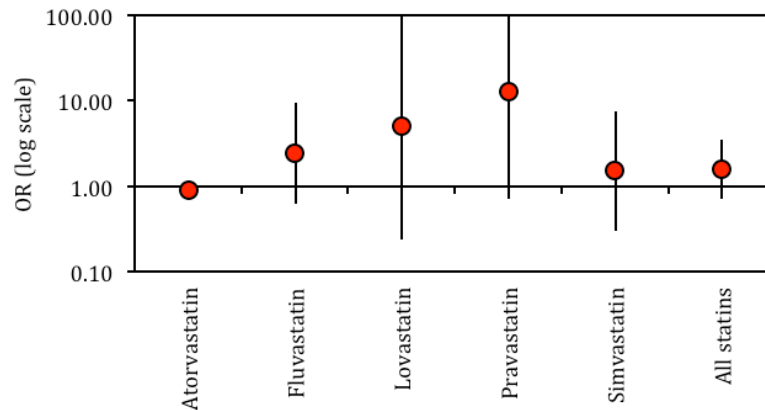


\* Estimates shown are ORs and 95% CIs.

Among individuals with established coronary heart disease, 10,704 participants contributed information on 296 myalgia events. There was one trial of atorvastatin with 270 events among 4,731 individuals; one trial of fluvastatin with 10 events among 834 participants; one trial of lovastatin with two events among 247 participants; one trial of pravastatin with six events among 4,271 participants; and one trial of simvastatin with eight events among 621 trial participants. There were no trials of rosuvastatin in this population.

In the secondary prevention population, statin therapy was not associated with a significant increase in the risk of incident myalgia events (OR: 1.61, 95% CI: 0.73, 3.58,  $I^2=40.1\%$ ) when compared to control (Figure 6.11). Although individuals with established coronary heart disease randomized to statins experienced numerically more myalgia events (except for atorvastatin), none of the individual statins had a statistically detectable effect on myalgia occurrence in this population: atorvastatin (OR: 0.91, 95% CI: 0.71, 1.16,  $I^2=0.0\%$ ); fluvastatin (OR: 2.45, 95% CI: 0.63, 9.54,  $I^2=0.0\%$ ); lovastatin (OR: 5.12, 95% CI: 0.24, 107.82,  $I^2=0.0\%$ ); pravastatin (OR: 13.01, 95% CI: 0.73, 231.02,  $I^2=0.0\%$ ); and simvastatin (OR: 1.51, 95% CI: 0.30, 7.53,  $I^2=0.0\%$ ).

**Figure 6.11** – Effect of statins compared to control on myalgia occurrence in the secondary prevention population.\*

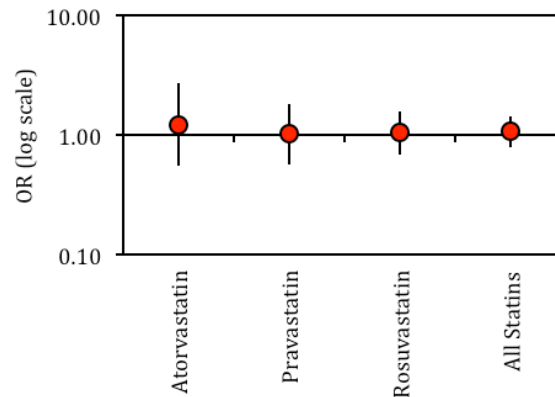


\* Estimates shown are ORs and 95% CIs. There were no trials of rosuvastatin among individuals with established coronary heart disease.

Among individuals with no prior coronary heart disease, 13,262 participants contributed information on 358 myalgia events. There were two trials of atorvastatin with 188 events among 5,248 individuals; three trials of pravastatin with 47 events among 7,030 participants; and one trial of rosuvastatin with 123 events among 984 trial participants. There were no trials of fluvastatin, lovastatin, and simvastatin in this population.

As shown in Figure 6.12, statin therapy was not associated with a significant increase in the risk of incident myalgia events in the primary prevention population (OR: 1.08, 95% CI: 0.81, 1.44,  $I^2=25.2\%$ ). Among individual statins, there were no statistically detectable effects of statins on incident myalgia: atorvastatin (OR: 1.22, 95% CI: 0.56, 2.75,  $I^2=83.5\%$ ); pravastatin (OR: 1.04, 95% CI: 0.58, 1.85,  $I^2=0.0\%$ ); rosuvastatin (OR: 1.06, 95% CI: 0.69, 1.61,  $I^2=0.0\%$ ).

**Figure 6.12** – Effect of statins compared to control on myalgia occurrence in the primary prevention population.\*



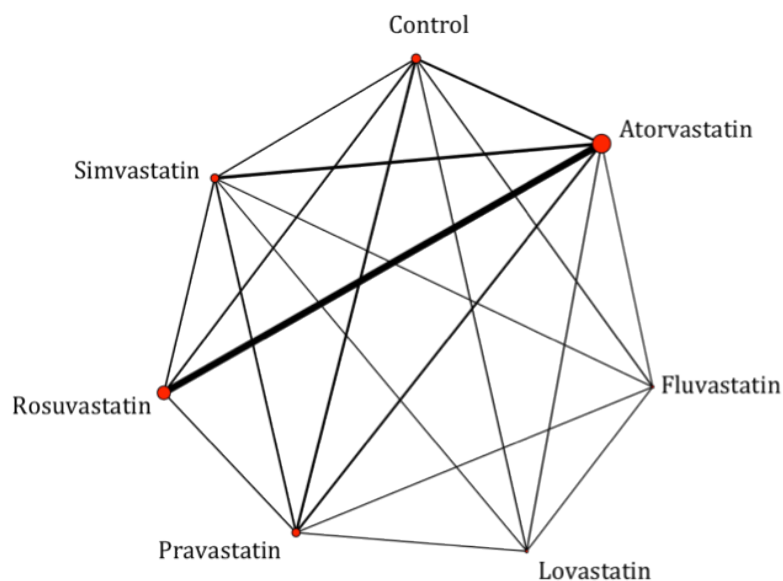
\* Estimates shown are ORs and 95% CIs. There were no trials of fluvastatin, lovastatin, and simvastatin among individuals with no established coronary heart disease at baseline.

#### 6.4.2 Comparative Harms of Individual Statins: Findings of the Network Meta-analysis

The network of eligible comparisons for this analysis is shown in Figure 6.13. In addition to the placebo-controlled trials included in the pair-wise meta-analyses, there were 45 direct head-to-head comparisons between statins including 1,295 events among 52,046 individuals that were not included in previous comparisons in the literature. Atorvastatin was directly compared to fluvastatin in one trial including 2,379 individuals (OR: 0.88, 95% CI: 0.47, 1.65,  $I^2=0.0\%$ ); to lovastatin in two trials including 3,027 individuals (OR: 0.86, 95% CI: 0.46, 1.51,  $I^2=11.7\%$ ); to pravastatin in five trials including 8,122 individuals (OR: 1.12, 95% CI: 0.84, 1.49,  $I^2=0.0\%$ ); to rosuvastatin in 21 trials including 13,354 individuals (OR: 0.88, 95% CI: 0.72, 1.61,  $I^2=1.4\%$ ); and to simvastatin in eight trials including 16,479 individuals (OR: 1.29, 95% CI: 0.74, 2.22,  $I^2=57.7\%$ ). Fluvastatin was directly compared to lovastatin in one trial including 953 individuals (OR: 1.18, 95% CI: 0.53, 2.67,  $I^2=0.0\%$ ); to pravastatin in one trial including 939 individuals (OR: 1.05, 95% CI: 0.47, 2.33,  $I^2=0.0\%$ ); and to simvastatin in one trial including 945 individuals (OR: 0.66, 95% CI: 0.32, 1.36,  $I^2=0.0\%$ ). Lovastatin was directly compared to pravastatin in one trial including 932 individuals (OR: 0.89, 95% CI: 0.39, 2.03,  $I^2=0.0\%$ ); and to simvastatin in one trial including 946 individuals (OR: 0.66, 95% CI: 0.32, 1.36,  $I^2=0.0\%$ ). There was one direct comparison between pravastatin and rosuvastatin including 832 individuals (OR: 0.66, 95% CI: 0.25, 1.77,  $I^2=0.0\%$ ); and three direct comparisons between pravastatin and simvastatin, including 1,815 individuals (OR: 0.77, 95% CI: 0.41, 1.45,  $I^2=0.0\%$ ). Finally, rosuvastatin was directly compared to simvastatin in two trials including 1,319 individuals, which suggested that

individuals randomized to rosuvastatin were statistically significantly more likely to experience myalgia events as compared to those randomized to simvastatin (OR: 2.85, 95% CI: 1.01, 8.33,  $I^2=0.0\%$ ).

**Figure 6.13** – Network of available comparisons for determining the comparative effects of individual statins on myalgia occurrence.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

In the base-case network meta-analysis, 53 trials provided information on myalgia events. In total, 82,769 individuals were included in the base-case analysis, which provided information on 1,884 events. In the base-case analysis, there were no significant differences between statins in terms of their effect on incident myalgia events when all trials of primary prevention, secondary prevention, and mixed patient populations were pooled (overall population) (Table 6.5). Although the direction and magnitude of the difference between rosuvastatin and simvastatin observed in the base-case network meta-analysis was consistent with the finding from the pair-wise meta-analysis, there was greater variability around this estimate when all eligible direct and indirect trials were combined; there was no statistically detectable difference between these two agents (OR of rosuvastatin vs. simvastatin: 1.46, 95% CrI: 0.98, 2.14). Although not statistically significant, simvastatin appeared to result in numerically fewer myalgia events as compared to other statins.

**Table 6.5** – Comparative tolerability of individual statins on myalgia events across all populations.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	1.08 (0.56, 2.17)	0.87 (0.54, 1.46)	1.10 (0.77, 1.53)	0.88 (0.71, 1.08)	1.28 (0.88, 1.80)
<b>Fluvastatin vs.</b>	-	0.81 (0.37, 1.71)	1.02 (0.48, 2.02)	0.82 (0.40, 1.58)	1.19 (0.56, 2.37)
<b>Lovastatin vs.</b>	-	-	1.26 (0.70, 2.15)	1.00 (0.58, 1.68)	1.46 (0.80, 2.54)
<b>Pravastatin vs.</b>	-	-	-	0.80 (0.55, 1.19)	1.17 (0.74, 1.82)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.46 (0.98, 2.14)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

There were no statistically detectable differences among individual statins in terms of increasing the risk of incident myalgia events in the secondary prevention of cardiovascular disease (Table 6.6). There was considerable uncertainty around the comparative estimates of lovastatin due to the very few number of data points available for this statin.

**Table 6.6** – Comparative effects of individual statins on myalgia events in the secondary prevention population.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	0.40 (0.06, 3.13)	0.16 (0.00, 5.37)*	0.72 (0.23, 1.98)	0.94 (0.56, 1.54)	1.62 (0.82, 2.95)
<b>Fluvastatin vs.</b>	-	0.39 (0.00, 18.45)*	1.80 (0.17, 14.78)	2.36 (0.28, 17.49)	4.04 (0.47, 30.42)
<b>Lovastatin vs.</b>	-	-	4.38 (0.11, 1346.8)*	5.88 (0.17, 1737.32)*	9.88 (0.29, 2902.76)*
<b>Pravastatin vs.</b>	-	-	-	1.30 (0.43, 4.55)	2.23 (0.69, 8.21)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.73 (0.73, 3.74)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right. There were too few data points to obtain reliable estimates for the comparative effects of lovastatin.

There were also no statistically detectable differences among individual statins in the primary prevention population (Table 6.7). Data were particularly sparse for this analysis with no trials of fluvastatin, lovastatin, and simvastatin among individuals without coronary heart disease.

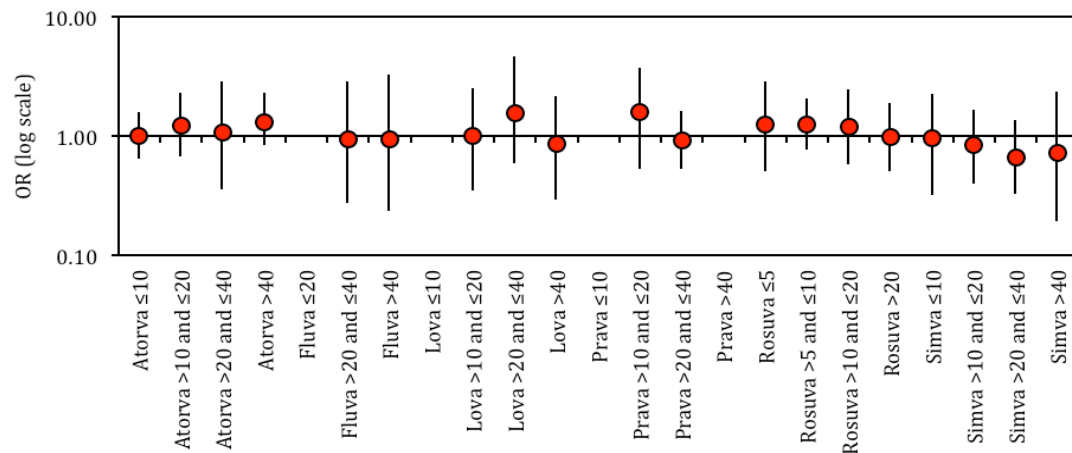
**Table 6.7** – Comparative effects of individual statins on myalgia events in the primary prevention population.\*

	<b>Pravastatin</b>	<b>Rosuvastatin</b>
<b>Atorvastatin vs.</b>	1.07 (0.24, 4.86)	0.93 (0.39, 2.04)
<b>Pravastatin vs.</b>	-	0.87 (0.17, 3.98)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right. There were no trials of fluvastatin, lovastatin, and simvastatin among individuals with no established coronary heart disease.

In the dose-level network meta-analysis that included all placebo-controlled, active-comparator, and dose-comparison trials reporting myalgia outcomes, a total of 95,052 participants experiencing 1,441 myalgia events in 59 trials were included. There were no statistically detectable differences between individual statins at different doses and control treatment. There was also a lack of an apparent dose-response relationship for myalgia (individuals randomized to higher doses of statins did not experience an increase in the odds of incident myalgia as compared to those randomized to lower doses) (Figure 6.14). In the case of rosuvastatin, individuals receiving up to 5 mg/day experienced numerically more myalgia events (OR of rosuvastatin  $\leq$ 5 mg/day vs. control: 1.26, 95 CrI: 0.51, 2.88) as compared to those receiving higher than 20 mg/day (OR of rosuvastatin  $>$ 20 mg/day vs. control: 0.99, 95% CrI: 0.52, 1.91). Similarly, individuals randomized to receive higher doses of simvastatin (OR of simvastatin  $\leq$ 10 mg/day vs. control: 0.95, 95% CrI: 0.33, 2.28) had numerically fewer myalgia events as compared to those receiving higher doses (OR of simvastatin  $>$ 40 mg/day vs. control: 0.72, 95% CrI: 0.19, 2.38).

**Figure 6.14** – Dose-specific analysis findings: comparative effects of individual statins compared to control for myalgia occurrence across all populations.\*



\* Estimates shown are ORs and 95% CrIs. There was no available data for the lowest doses of fluvastatin, lovastatin, and pravastatin. Similarly, no data was available for pravastatin at higher than 40 mg/day.

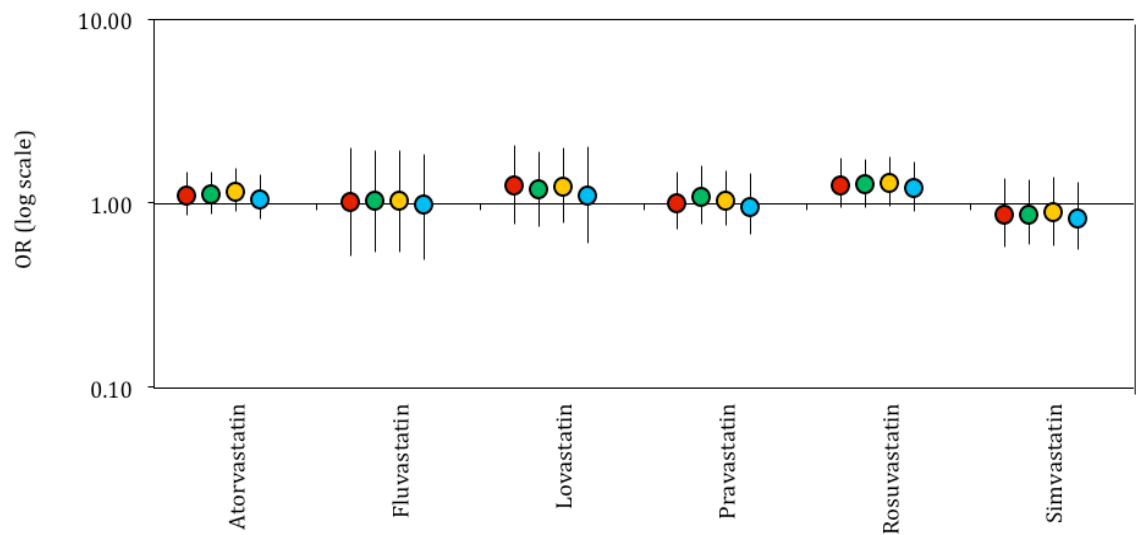
#### 6.4.3 Investigation of Heterogeneity and Inconsistency in the Network Meta-analysis

Meta-regression analyses evaluating the impact of mean age at baseline, mean LDL-cholesterol concentration at baseline, and publication year could not explain the potential heterogeneity and inconsistency in the base-case network meta-analysis. Table 6.8 shows the between-study heterogeneity and covariate coefficients in various meta-regression analyses. Figure 6.15 shows the sensitivity of the relative treatment effects of statins vs. control to different meta-regression analyses. According to this figure, the comparative effects of individual statins on myalgia events were not sensitive to mean age at baseline, mean LDL cholesterol concentrations at baseline, and publication year. Statistical exploration of inconsistency did not detect any discrepancy between direct and indirect evidence within closed loops in the network (see *Appendix*).

**Table 6.8** – Findings of the meta-regression analyses for myalgia.

	Between-study heterogeneity (standard deviation)	Meta-regression coefficient estimate, log scale (95% CrI)
Base-case analysis	0.2730	-
Meta-regression analysis adjusting for mean age at baseline	0.2546	-0.02 (-0.1, 0.06)
Meta-regression analysis adjusting for LDL concentration at baseline	0.2475	-0.03 (-0.08, 0.01)
Meta-regression analysis adjusting for publication year	0.2554	0.01 (0.00, 0.02)

**Figure 6.15** – Sensitivity of the base-case findings to meta-regression analyses for myalgia.\*



\* Estimates shown are ORs and 95% CrIs. Base-case results are shown in red, while the analysis adjusted for mean age of patients at baseline is shown in green, the analysis adjusting for the mean LDL cholesterol concentration at baseline is shown in yellow, and the analysis adjusting for publication year is shown in blue.

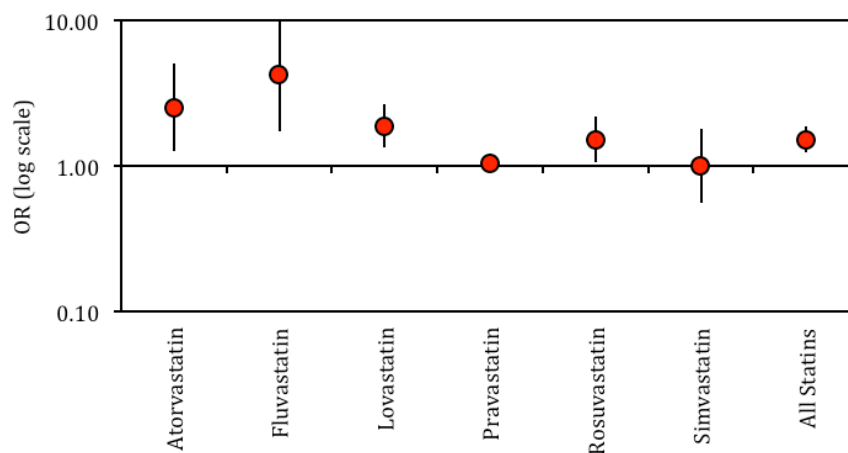
## 6.5 Outcome 3: Transaminase Elevations

### 6.5.1 Harms of Statins vs. Control: Findings of the Traditional Pair-wise Meta-analysis

Across all populations, 122,665 participants contributed information on 1,619 transaminase elevations. There were six trials with 190 events among 14,973 individuals; three trials of fluvastatin with 31 events among 3,225 individuals; four trials of lovastatin with 286 events among 15,501 individuals; 10 trials of pravastatin with 737 events among 33,232 participants; five trials of rosuvastatin with 158 events among 28,640 individuals; and six trials of simvastatin with 217 events among 27,094 participants.

Overall, as shown in Figure 6.16, statin therapy was associated with an increase in the risk of transaminase elevations (OR: 1.51, 95% CI: 1.24, 1.84,  $I^2=52.3\%$ ) when compared to control (see the *Appendix* for trial-level results). Atorvastatin (OR: 2.50, 95% CI: 1.25, 5.02,  $I^2=69.5\%$ ); fluvastatin (OR: 4.21, 95% CI: 1.72, 10.32,  $I^2=0.0\%$ ); lovastatin (OR: 1.88, 95% CI: 1.34, 2.63,  $I^2=0.0\%$ ); and rosuvastatin (OR: 1.52, 95% CI: 1.06, 2.18,  $I^2=10.6\%$ ) were associated with significantly higher odds of transaminase elevations as compared to control treatment. Individuals randomized to pravastatin (OR: 1.04, 95% CI: 0.90, 1.20,  $I^2=0.0\%$ ) and simvastatin (OR: 1.00, 95% CI: 0.55, 1.80,  $I^2=49.4\%$ ) did not experience significantly more transaminase elevations as compared to those randomized to control treatment. According to contour-enhanced funnel plots, there was no evidence of small study effects (see *Appendix*).

**Figure 6.16** – Effect of statins compared to control treatment on transaminase elevations across all populations.\*

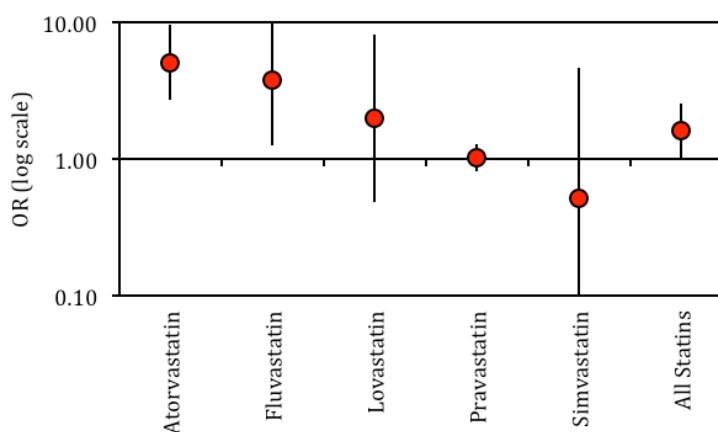


\* Estimates shown are ORs and 95% CIs.

Among individuals with established coronary heart disease, 27,336 individuals contributed information on 639 transaminase elevations. There were two trials of atorvastatin with 69 events among 6,331 individuals; two trials of fluvastatin with 19 events among 1,996 individuals; two trials of lovastatin with nine events among 651 individuals; three trials of pravastatin with 292 events among 13,293 participants; and two trials of simvastatin with 130 events among 5,065 individuals. There were no trials of rosuvastatin in this population.

In the secondary prevention population, statin therapy was associated with a significant increase in the risk of transaminase elevations (OR: 1.60, 95% CI: 1.02, 2.51,  $I^2=69.0\%$ ). Among individual statins, atorvastatin (OR: 5.00, 95% CI: 2.66, 9.46,  $I^2=0.0\%$ ) and fluvastatin (OR: 3.77, 95% CI: 1.24, 11.43,  $I^2=0.0\%$ ) were significantly associated with an increase in transaminase elevations whereas lovastatin (OR: 1.98, 95% CI: 0.48, 8.15,  $I^2=0.0\%$ ); pravastatin (OR: 1.01, 95% CI: 0.81, 1.26,  $I^2=0.0\%$ ); and simvastatin (OR: 0.51, 95% CI: 0.06, 4.64,  $I^2=76.0\%$ ) were not (Figure 6.17).

**Figure 6.17** – Effect of statins compared to control on transaminase elevations in the secondary prevention population.\*

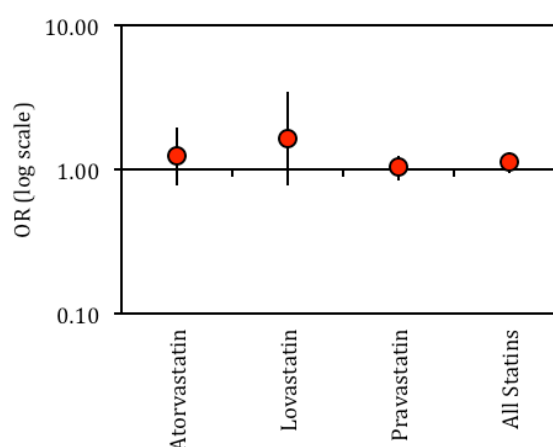


\* Estimates shown are ORs and 95% CIs.

Among individuals with no prior coronary heart disease, 45,838 individuals contributed information on 554 transaminase elevations. There were two trials of atorvastatin with 62 events among 5,248 participants; one trial of lovastatin with 29 events among 6,605 individuals; and four trials of pravastatin with 394 events among 15,199 participants. There were no trials of fluvastatin and simvastatin in this population.

In the primary prevention population, as shown in Figure 6.18, statin therapy was not associated with a significant increase in the risk of transaminase elevation (OR: 1.12, 95% CI: 0.95, 1.33,  $I^2=0.0\%$ ) as compared to control treatment. Among statins, individuals randomized to atorvastatin (OR: 1.24, 95% CI: 0.78, 1.98,  $I^2=0.0\%$ ); lovastatin (OR: 1.64, 95% CI: 0.77, 3.49,  $I^2=0.0\%$ ); and pravastatin (OR: 1.03, 95% CI: 0.84, 1.26,  $I^2=0.0\%$ ) did not have an increase in the odds of experiencing transaminase elevations as compared to those randomized to control.

**Figure 6.18** – Effect of statins compared to control treatment on transaminase elevations in the primary prevention population.\*



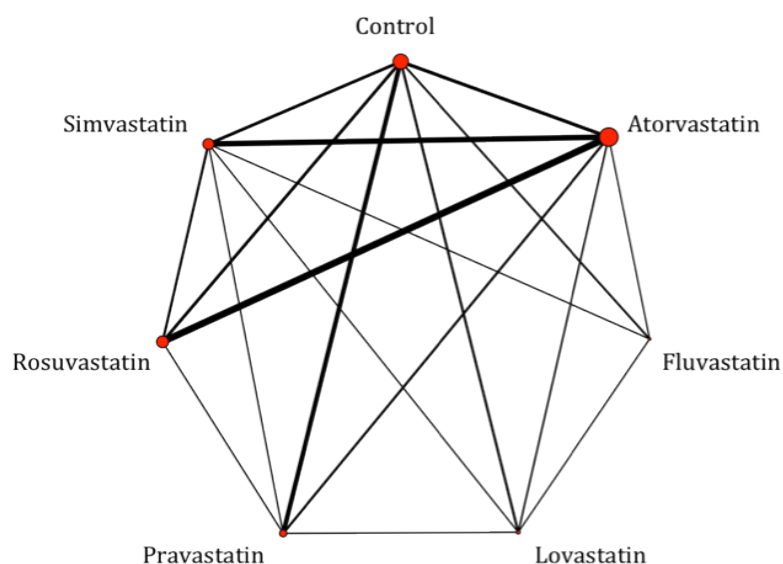
\* Estimates shown are ORs and 95% CIs. There were no trials of fluvastatin, rosuvastatin, and simvastatin among individuals with no established coronary heart disease.

### 6.5.2 Comparative Harms of Individual Statins: Findings of the Network Meta-analysis

The network of eligible comparisons for this analysis is shown in Figure 6.19. In addition to the placebo-controlled trials included in the traditional pair-wise meta-analyses, there were 46 direct head-to-head comparisons between statins including 44,755 individuals that were not included in previous analyses available in the literature. Atorvastatin was compared to fluvastatin in one trial including 154 individuals (OR: 0.19, 95% CI: 0.01, 4.02,  $I^2=0.0\%$ ); to lovastatin in one trial including 749 individuals, which suggested that individuals randomized to atorvastatin experienced significantly fewer transaminase elevations as compared to those receiving lovastatin; however this finding was based only on four events (OR: 0.07, 95% CI: 0.00, 0.71,  $I^2=0.0\%$ ); to pravastatin in four trials including 6,321 participants, which demonstrated that atorvastatin resulted in significantly higher odds of transaminase elevations as compared to pravastatin (OR: 3.70, 95% CI: 1.35, 10.00,  $I^2=61.3\%$ ); to rosuvastatin in 17 trials including

11,283 individuals (OR: 1.35, 95% CI: 0.75, 2.44,  $I^2=37.0\%$ ); and to simvastatin in 12 trials including 20,825 individuals (OR: 1.64, 95% CI: 0.76, 3.44,  $I^2=52.9\%$ ). Fluvastatin was directly compared to lovastatin in one trial including 154 trial participants (OR: 5.27, 95% CI: 0.25, 111.56,  $I^2=0.0\%$ ), and to simvastatin in one trial including 152 individuals (OR: 5.13, 95% CI: 0.24, 108.75,  $I^2=0.0\%$ ). Lovastatin was directly compared to pravastatin in one trial including 672 individuals (OR: 0.33, 95% CI: 0.03, 3.12,  $I^2=0.0\%$ ), and to simvastatin in one trial (the direct comparison between lovastatin and simvastatin included zero events therefore the number of trial participants were not counted towards the total). Pravastatin was directly compared to rosuvastatin in one trial including 366 individuals (OR: 0.18, 95% CI: 0.01, 3.45,  $I^2=0.0\%$ ), and to simvastatin in one trial including 265 individuals (OR: 0.19, 95% CI: 0.01, 3.93,  $I^2=0.0\%$ ). Rosuvastatin was directly compared to simvastatin in four trials including 3,904 individuals (OR: 1.05, 95% CI: 0.35, 3.13,  $I^2=0.0\%$ ).

**Figure 6.19** – Network of available comparisons for determining the comparative effects of individual statins on transaminase elevations.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

In the base-case network meta-analysis, 70 trials provided information on the occurrence of transaminase elevations. In total, there were 2,051 elevations among 163,248 trial participants. When all eligible trials were pooled (overall population), there were statistically detectable

differences between individual statins (Table 6.9). Individuals randomized to receive atorvastatin were more likely to experience transaminase elevations as compared to those randomized to receive pravastatin (OR: 2.55, 95% CrI: 1.54, 4.14); rosuvastatin (OR: 1.60, 95% CrI: 1.06, 2.38); and simvastatin (OR: 2.20, 95% CrI: 1.36, 3.52). Fluvastatin appeared to significantly increase the odds of transaminase elevations as compared to pravastatin (OR: 5.19, 95% CrI: 1.75, 16.73); rosuvastatin (OR: 3.25, 95% CrI: 1.08, 10.50); and simvastatin (OR: 4.50, 95% CrI: 1.49, 14.19). Although not statistically significant, fluvastatin resulted in numerically more transaminase elevations than atorvastatin (OR: 2.04, 95% CrI: 0.70, 6.66) (the reciprocal is provided in Table 6.9).

**Table 6.9** – Comparative effects of individual statins on transaminase elevations across all populations.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	0.49 (0.15, 1.42)	1.26 (0.57, 2.73)	2.55 (1.54, 4.14)	1.60 (1.06, 2.38)	2.20 (1.36, 3.52)
<b>Fluvastatin vs.</b>	-	2.58 (0.76, 9.03)	5.19 (1.75, 16.73)	3.25 (1.08, 10.50)	4.50 (1.49, 14.19)
<b>Lovastatin vs.</b>	-	-	2.03 (0.90, 4.56)	1.27 (0.55, 2.93)	1.76 (0.75, 4.12)
<b>Pravastatin vs.</b>	-	-	-	0.63 (0.36, 1.10)	0.87 (0.47, 1.57)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.38 (0.79, 2.38)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

Among participants with established coronary heart disease, as shown in Table 6.10, atorvastatin was associated with a significant increase in the risk of transaminase elevations as compared to pravastatin (OR: 3.97, 95% CrI: 1.25, 12.55); and simvastatin (OR: 4.04, 95% CrI: 1.37, 11.73). Consistent with the findings obtained from the overall population, fluvastatin resulted in significantly more transaminase elevations as compared to pravastatin (OR: 6.55, 95% CrI: 1.21, 42.32) and simvastatin (OR: 6.67, 95% CrI: 1.21, 43.33). There were too few data points available for fluvastatin, which resulted in considerably wide credible intervals around its relative treatment effects.

**Table 6.10** – Comparative effects of individual statins on transaminase elevations in the secondary prevention population.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	0.60 (0.10, 2.99)	1.94 (0.28, 12.95)	3.97 (1.25, 12.55)	2.19 (0.67, 7.16)	4.04 (1.37, 11.73)
<b>Fluvastatin vs.</b>	-	3.21 (0.42, 28.98)	6.55 (1.21, 42.32)	3.63 (0.49, 31.82)	6.67 (1.21, 43.33)
<b>Lovastatin vs.</b>	-	-	2.02 (0.29, 14.71)	1.12 (0.12, 11.27)	2.09 (0.29, 15.35)
<b>Pravastatin vs.</b>	-	-	-	0.55 (0.10, 2.91)	1.02 (0.25, 4.12)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.83 (0.37, 9.05)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

As shown in Table 6.11, there were no statistically detectable differences among individual statins. Although atorvastatin appeared to result in numerically more transaminase elevations than lovastatin (OR: 1.12, 95% CrI: 0.29, 5.86), pravastatin (OR: 1.92, 95% CrI: 0.97, 6.84), and rosuvastatin (OR: 1.27, 95% CrI: 0.62, 3.14), these findings were associated with considerable uncertainty due to the very small number of events included in this analysis.

**Table 6.11** – Comparative effects of individual statins on transaminase elevations in the primary prevention population.\*

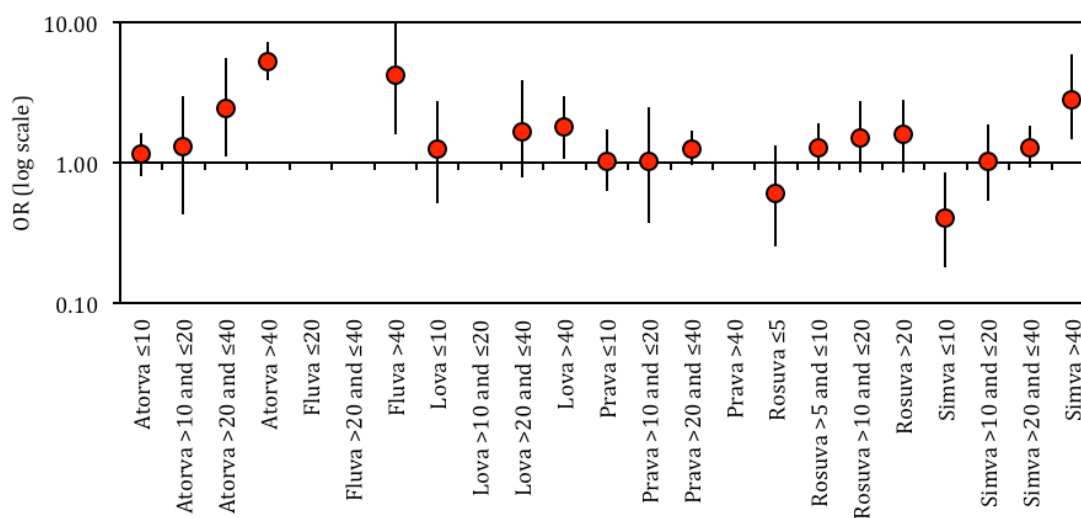
	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>
<b>Atorvastatin vs.</b>	1.12 (0.29, 5.86)	1.92 (0.97, 6.84)	1.27 (0.62, 3.14)
<b>Lovastatin vs.</b>	-	1.72 (0.47, 8.86)	1.13 (0.24, 4.98)
<b>Pravastatin vs.</b>	-	-	0.66 (0.20, 1.47)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right. There were no trials of fluvastatin and simvastatin among individuals without established coronary heart disease.

In the dose-specific analysis for clinically meaningful elevations in hepatic transaminases included all placebo-controlled, active-comparator, and dose-comparison trials, there was a total of 2,287 transaminase elevations among 185,600 participants in 84 trials. A number of statins at

high doses were associated with significantly higher odds of transaminase elevations as compared to control treatment (Figure 6.20): atorvastatin at >20 and ≤40 mg/day (OR: 2.42, 95% CrI: 1.10, 5.50) and at >40 mg/day (OR: 5.25, 95% CrI: 3.89, 7.24); fluvastatin at >40 mg/day (OR: 4.16; 95% CrI: 1.60, 14.36); lovastatin at >40 mg/day (OR: 1.80, 95% CrI: 1.06, 2.97); and simvastatin at >40 mg/day (OR: 2.83, 95% CrI: 1.47, 5.87). Surprisingly, simvastatin at ≤10 mg/day resulted in lower odds of transaminase elevations as compared to control (OR: 0.41, 95% CrI: 0.18, 0.85). There was a general dose-response relationship, which was particularly clear with atorvastatin, rosuvastatin, and simvastatin, with higher doses resulting in higher odds of transaminase elevations.

**Figure 6.20** – Dose-specific analysis findings: comparative effects of individual statins compared to control for transaminase elevations across all populations.\*



\* Estimates shown are ORs and 95% CrIs. There were no trials of fluvastatin at low and moderate doses; lovastatin at low doses; and pravastatin at high doses.

### 6.5.3 Investigation of Heterogeneity and Inconsistency in the Network Meta-analysis

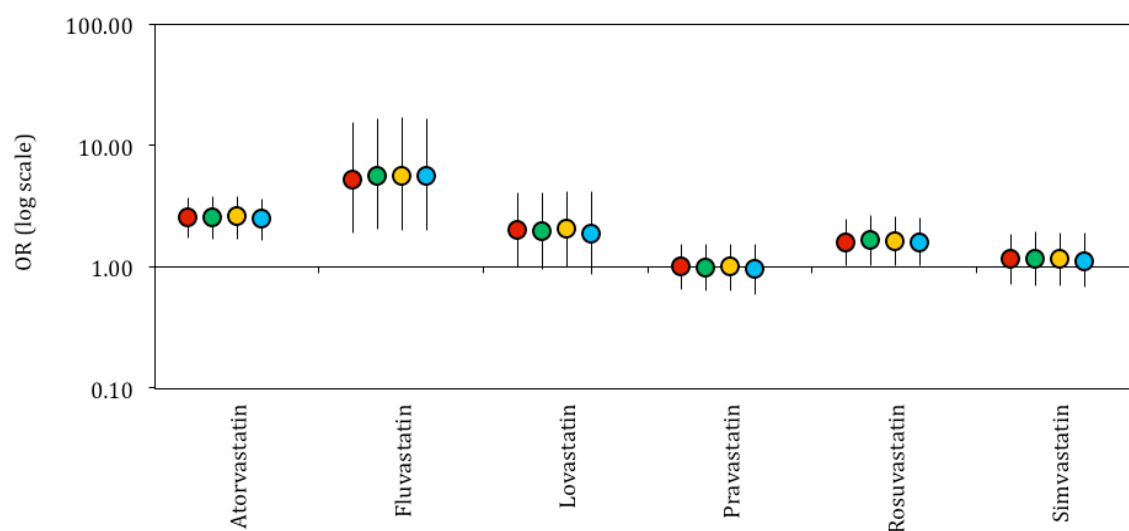
Meta-regression analyses evaluating the impact of mean age at baseline, mean LDL cholesterol concentration at baseline, and publication year could not explain the potential heterogeneity and inconsistency in the base-case network meta-analysis. Table 6.12 shows the between-study heterogeneity and covariate coefficients obtained in various meta-regression analyses. Figure 6.21 shows the sensitivity of relative treatment effects of individual statins vs. control treatment to different meta-regression analyses. According to this figure, the comparative benefits of individual statins were not sensitive to mean age at baseline, mean LDL cholesterol

concentration at baseline and publication year. There was statistically detectable inconsistency within the closed loop of atorvastatin, lovastatin, and pravastatin, which was likely explained by dose differences among individual statins (see *Appendix*).

**Table 6.12** – Findings of the meta-regression analysis for transaminase elevations.

	Between-study heterogeneity (standard deviation)	Meta-regression coefficient estimate log scale (95% CrI)
Base-case analysis	0.5838	-
Meta-regression analysis adjusting for mean age at baseline	0.6005	-0.02 (-0.11, 0.07)
Meta-regression analysis adjusting for baseline LDL concentration	0.5963	0.00 (-0.01, 0.02)
Meta-regression analysis adjusting for publication year	0.5921	-0.02 (-0.10, 0.07)

**Figure 6.21** – Sensitivity of the base-case findings to meta-regression analyses for transaminase elevations.\*



\* Estimates shown are ORs and 95% CrIs. Base-case results are shown in red, while the analysis adjusting for mean age of patients at baseline is shown in green, the analysis adjusting for the mean LDL cholesterol concentration at baseline is shown in yellow, and the analysis adjusting for publication year is shown in blue.

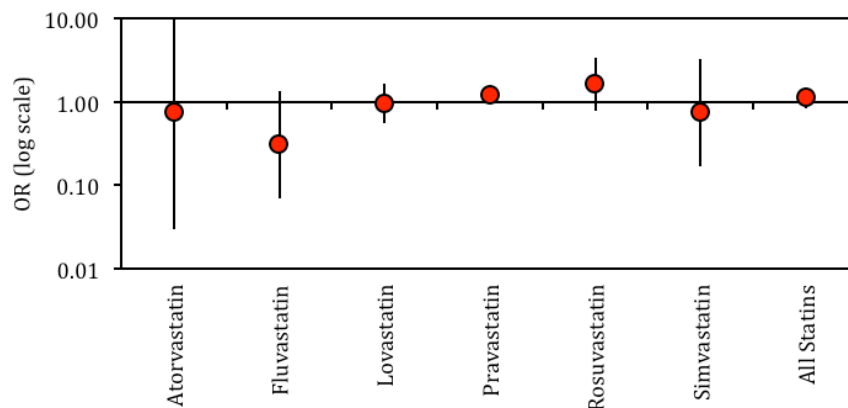
## 6.6 Outcome 4: Creatine Kinase Elevations

### 6.6.1 Harms of Statins vs. Control: Findings of the Traditional Pair-wise Meta-analysis

In the traditional pair-wise meta-analysis of statin therapy vs. control across all populations, 101,324 participants contributed information on 463 creatine kinase elevations (see the *Appendix* for trial-level results). There were two trials of atorvastatin with 14 events among 7,569 individuals; four trials of fluvastatin with eight events among 2,646 individuals; three trials of lovastatin with 72 events among 15,254 individuals; seven trials of pravastatin with 281 events among 20,690 individuals; five trials of rosuvastatin with 58 events among 28,640 individuals; and five trials of simvastatin with 30 events among 26,525 trial participants.

Overall, as shown in Figure 6.22, statin therapy was not associated with an increase in the risk of creatine kinase elevations (OR: 1.13, 95% CI: 0.85, 1.51,  $I^2=20.4\%$ ) when compared to control (Figure 6.22) (see the *Appendix* for trial-level results). None of the individual statins resulted in significantly higher odds of creatine kinase elevations: atorvastatin (OR: 0.75, 95% CI: 0.03, 17.61,  $I^2=71.6\%$ ); fluvastatin (OR: 0.31, 95% CI: 0.07, 1.33,  $I^2=0.0\%$ ); lovastatin (OR: 0.75, 95% CI: 0.55, 1.63,  $I^2=9.2\%$ ); pravastatin (OR: 1.22, 95% CI: 0.96, 1.55,  $I^2=0.0\%$ ); rosuvastatin (OR: 1.62, 95% CI: 0.78, 3.39,  $I^2=14.6\%$ ); and simvastatin (OR: 0.74, 95% CI: 0.17, 3.28,  $I^2=57.7\%$ ). According to contour-enhanced funnel plots, there was no evidence of small study effects (see *Appendix*).

**Figure 6.22** – Effect of statins compared to control on creatine kinase elevations across all populations.\*

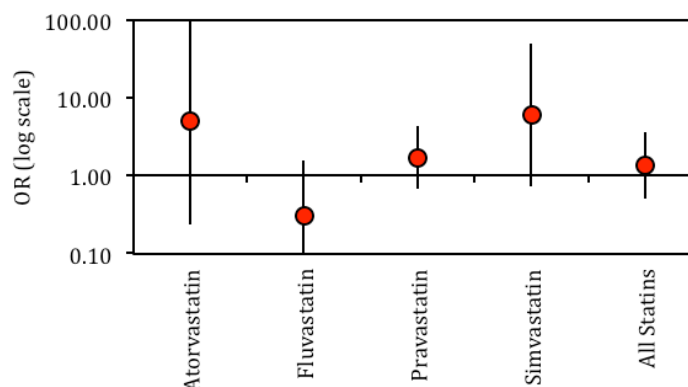


\* Estimates shown are ORs and 95% CIs.

Among individuals with established coronary heart disease (secondary prevention population), 15,895 trial participants contributed information on 35 clinically meaningful creatine kinase elevations. There was one trial of atorvastatin with two events among 4,731 participants; three trials of fluvastatin with seven events among 2,361; one trial of pravastatin with 19 events among 4,159 participants; and one trial of simvastatin with seven events among 4,444 participants. Lovastatin and rosuvastatin did not have any trials in this population.

In the secondary prevention population, statin therapy was not associated with a significant increase in the risk of creatine kinase elevations (OR: 1.36, 95% CI: 0.51, 3.61,  $I^2=22.4\%$ ) (Figure 6.23). None of the individual statins resulted in significantly higher odds of creatine kinase elevations: atorvastatin (OR: 5.01, 95% CI: 0.24, 104.53,  $I^2=0.0\%$ ); fluvastatin (OR: 0.31, 95% CI: 0.06, 1.56,  $I^2=0.0\%$ ); pravastatin (OR: 1.72, 95% CI: 0.67, 4.37,  $I^2=0.0\%$ ); and simvastatin (OR: 6.02, 95% CI: 0.72, 50.04,  $I^2=0.0\%$ ). In general, these results were associated with considerable uncertainty due to the scarcity of events and the small number of trials eligible for inclusion in this analysis.

**Figure 6.23** – Effect of statins compared to control on creatine kinase elevations in the secondary prevention population.\*



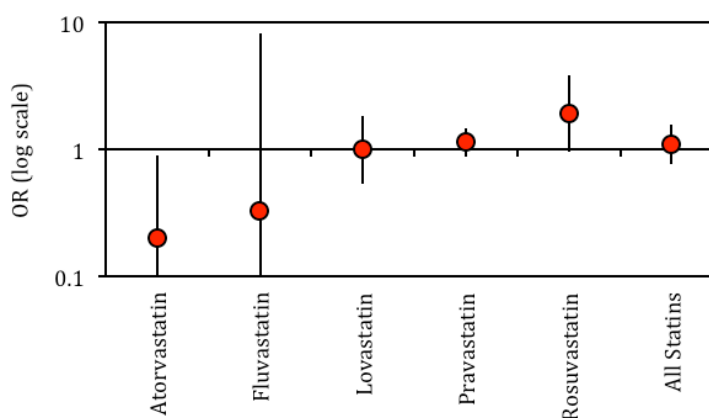
\* Estimates shown are ORs and 95% CIs. There were no trials of rosuvastatin among individuals with established coronary heart disease at baseline.

Among individuals with no prior coronary heart disease (primary prevention population), 43,713 trial participants contributed information on 339 clinically meaningful creatine kinase elevations. There was one trial of atorvastatin with 12 events among 2,838 individuals; one trial of fluvastatin with one event among 285 individuals; one trial of lovastatin with 42 events among 6,605 individuals; four trials of pravastatin with 238 events among 15,199 individuals;

and two trials of rosuvastatin with 46 events among 18,786 participants. There were no trials of simvastatin in this population.

Consistent with the findings obtained in the overall and secondary prevention populations, statin therapy was not associated with a significant increase in the risk of creatine kinase elevations (OR: 1.11, 95% CI: 0.78, 1.59,  $I^2=26.8\%$ ) as compared to control treatment (Figure 6.24). Similarly, fluvastatin (OR: 0.33, 95% CI: 0.01, 8.25,  $I^2=0.0\%$ ); lovastatin (OR: 1.00, 95% CI: 0.54, 1.83,  $I^2=0.0\%$ ); pravastatin (OR: 1.15, 95% CI: 0.89, 1.49,  $I^2=0.0\%$ ); and rosuvastatin (OR: 1.93, 95% CI: 0.96, 3.87,  $I^2=0.0\%$ ) did not result in higher odds of creatine kinase elevations. Surprisingly atorvastatin was associated with a significant decrease in the risk of creatine kinase elevations in this population (OR: 0.20, 95% CI: 0.04, 0.90,  $I^2=0.0\%$ ).

**Figure 6.24** – Effect of statins compared to control on creatine kinase elevations in the primary prevention population.\*



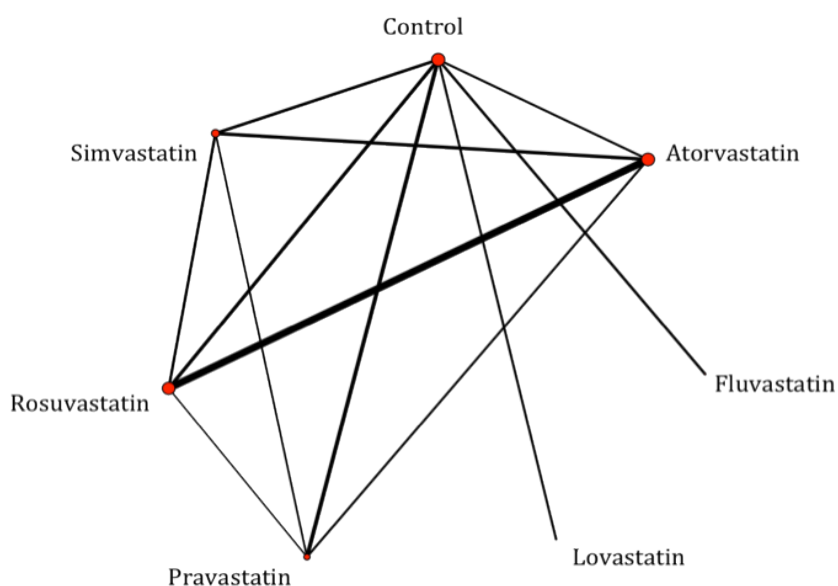
\* Estimates shown are ORs and 95% CIs. There were no trials of simvastatin among individuals with no established coronary heart disease at baseline.

#### 6.6.2 Comparative Harms of Individual Statins: Findings of the Network Meta-analysis

The network of eligible comparisons is shown in Figure 6.25. In addition to the trials included in the pair-wise comparisons of statin therapy vs. control, there were 30 direct head-to-head comparisons among individual statins, providing information on 229 events among 31,090 trial participants. Atorvastatin was directly compared to pravastatin in three trials with 127 events among 7,028 individuals (OR: 1.19, 95% CI: 0.84, 1.69,  $I^2=0.0\%$ ); to rosuvastatin in 16 trials with 56 events among 12,030 individuals (OR: 1.25, 95% CI: 0.72, 2.17,  $I^2=0.0\%$ ); and to simvastatin in five trials with 37 events among 6,555 individuals (OR: 0.77, 95% CI: 0.48, 1.92,  $I^2=0.0\%$ ). Pravastatin was directly compared to rosuvastatin in one trial with one event among 1,059

individuals (OR: 0.34, 95% CI: 0.01, 8.45,  $I^2=0.0\%$ ); and to simvastatin in one trial with two events among 550 individuals (OR: 0.19, 95% CI: 0.00, 4.16,  $I^2=0.0\%$ ). Finally, rosuvastatin was directly compared to simvastatin in four trials with six events among 3,868 trial participants (OR: 2.44, 95% CI: 0.53, 11.11,  $I^2=0.0\%$ ).

**Figure 6.25** – Network of available comparisons for determining the comparative effects of individual statins on creatine kinase elevations.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

In the base-case network meta-analysis, 49 trials provided information for the creatine kinase analysis. In total, 124,935 individuals were included in the base-case analysis, which provided information on 708 individuals with clinically meaningful creatine kinase elevations. In the base-case analysis that pooled all trials of primary prevention, secondary prevention, and mixed patient populations, individuals randomized to fluvastatin appeared to have significantly lower odds of experiencing creatine kinase elevations as compared to those randomized to atorvastatin (OR: 0.17, 95% CrI: 0.04, 0.82) (the reciprocal of this finding is reported in Table 6.13); pravastatin (OR: 0.20, 95% CrI: 0.04, 0.88); rosuvastatin (OR: 0.18, 95% CrI: 0.04, 0.81); and simvastatin (OR: 0.20, 95% CrI: 0.04, 0.94). Although fluvastatin appeared to result in fewer individuals experiencing creatine kinase elevations than lovastatin, this finding was not

statistically significant (OR: 0.24, 95% CrI: 0.05, 1.17). There were no other statistically detectable differences among statins (Table 6.13).

**Table 6.13** – Comparative effects of individual statins on creatine kinase elevations across all populations.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	5.59 (1.22, 25.52)	1.32 (0.54, 2.88)	1.13 (0.65, 1.78)	0.99 (0.64, 1.53)	1.13 (0.65, 1.97)
<b>Fluvastatin vs.</b>	-	0.24 (0.05, 1.17)	0.20 (0.04, 0.88)	0.18 (0.04, 0.81)	0.20 (0.04, 0.94)
<b>Lovastatin vs.</b>	-	-	0.84 (0.39, 1.94)	0.76 (0.34, 1.85)	0.86 (0.37, 2.23)
<b>Pravastatin vs.</b>	-	-	-	0.89 (0.51, 1.63)	1.01 (0.55, 2.00)
<b>Rosuvastatin vs.</b>	-	-	-	-	1.14 (0.62, 2.19)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

There were too few events for a reliable analysis in the secondary prevention population. Small number of events was also a complication for the network meta-analysis in the primary prevention population, with a number of analyses failing to converge due to the very small number of data points available for analysis. This was particularly the case for comparisons involving fluvastatin and simvastatin. There were no statistically detectable differences among individual statins in terms of the odds of creating kinase elevations in the primary prevention population (Table 6.14).

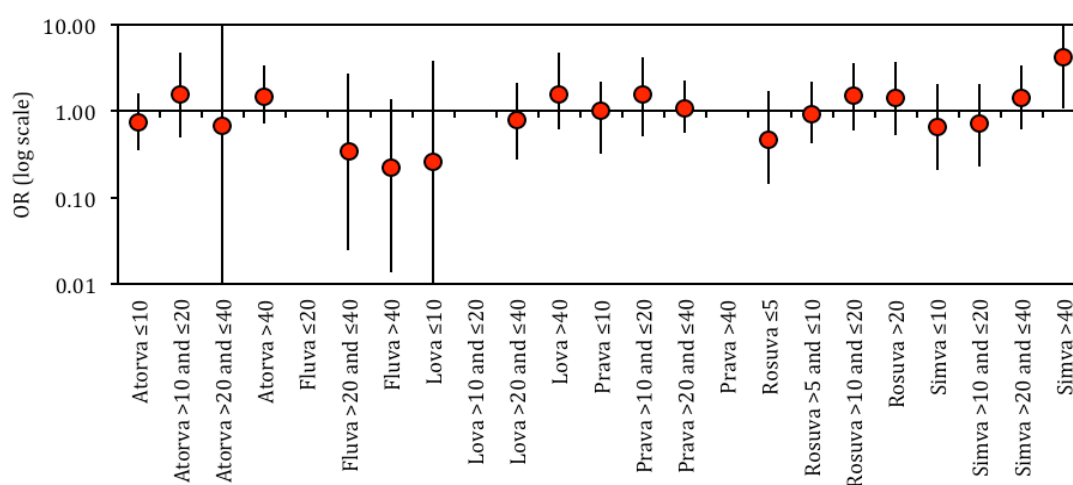
**Table 6.14** – Comparative effects of individual statins on creatine kinase elevations in the primary prevention population.\*

	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>
<b>Atorvastatin vs.</b>	0.75 (0.03, 18.56)	0.60 (0.05, 5.79)	0.55 (0.11, 2.64)
<b>Lovastatin vs.</b>	-	0.82 (0.04, 14.81)	0.74 (0.03, 17.57)
<b>Pravastatin vs.</b>	-	-	0.90 (0.11, 9.07)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right. There were no trials of fluvastatin and simvastatin among individuals with no established coronary heart disease at baseline.

In the dose-specific analysis that included all placebo-controlled, active-comparator, and dose-comparison trials, a total of 758 individuals with clinically meaningful creatine kinase elevations among 134,676 trial participants in 58 trials were included. There were no available data for fluvastatin at low doses, lovastatin at moderate doses, and pravastatin at high doses. There was a dose-response relationship with simvastatin, with higher doses resulting in higher odds of creatine elevations (Figure 6.26). Simvastatin at >40 mg/day resulted in significantly higher odds of experiencing elevations as compared to control treatment (OR: 4.14, 95% CrI: 1.08, 16.24).

**Figure 6.26** – Dose-specific analysis findings: comparative effects of individual statins compared to control for creatine kinase elevations across all populations.\*



\* Estimates shown are ORs and 95% CrIs.

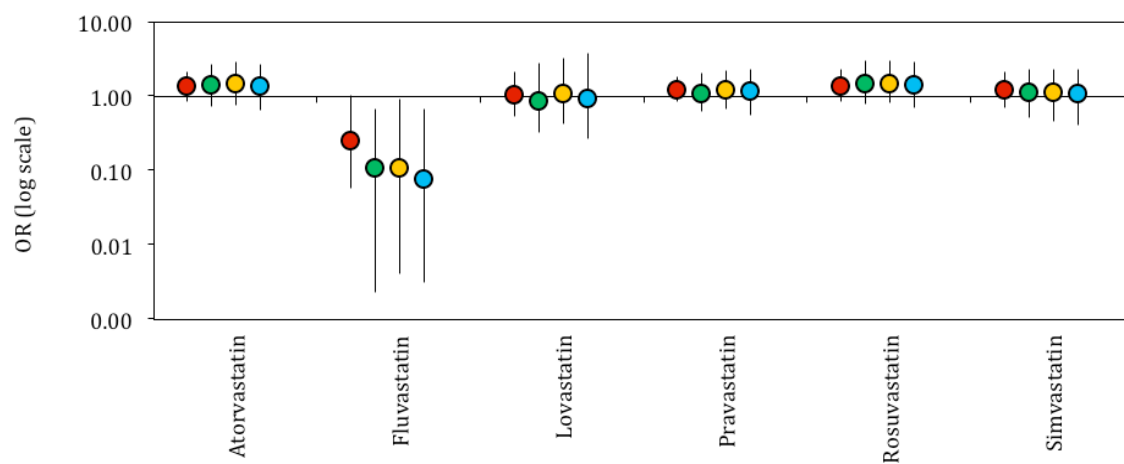
### 6.6.3 Investigation of Heterogeneity and Inconsistency in the Network Meta-analysis

Meta-regression analyses evaluating the impact of mean age at baseline, mean LDL-cholesterol concentration at baseline, and publication year could not explain the potential heterogeneity and inconsistency in the base-case network meta-analysis. In fact, heterogeneity appeared to increase in meta-regression analyses. Table 6.15 shows the between-study standard deviations and covariate coefficients obtained with the base-case adjusted analyses. Figure 6.27 shows the sensitivity of relative treatment effects of statins vs. control to different meta-regression analyses. According to this figure, the comparative effects of statins were not sensitive to differences across included studies in terms of mean age at baseline, mean LDL cholesterol concentration at baseline, and publication year. There was no statistically detectable inconsistency between direct and indirect evidence within closed loops in the treatment network (see *Appendix*).

**Table 6.15** – Findings of the meta-regression analyses for creatine kinase elevations.

	<b>Between-study heterogeneity (standard deviation)</b>	<b>Meta-regression coefficient estimate, log scale (95% CrI)</b>
Base-case analysis	0.2865	-
Meta-regression analysis adjusting for mean age at baseline	0.5007	-0.03 (-0.17, 0.08)
Meta-regression analysis adjusting for mean LDL concentration at baseline	0.5500	-0.11 (-0.31, 0.05)
Meta-regression analysis adjusting for publication year	0.6229	0.02 (-0.01, 0.04)

**Figure 6.27** – Sensitivity of the base-case findings to meta-regression analyses for creatine kinase elevations.\*



\* Estimates shown are ORs and 95% CrIs. Base-case results are shown in red, while the analysis adjusting for mean age of patients at baseline is shown in green, the analysis adjusting for the mean LDL cholesterol concentration at baseline is shown in yellow, and the analysis adjusting for publication year is shown in blue.

## 6.7 Secondary Harm Outcomes

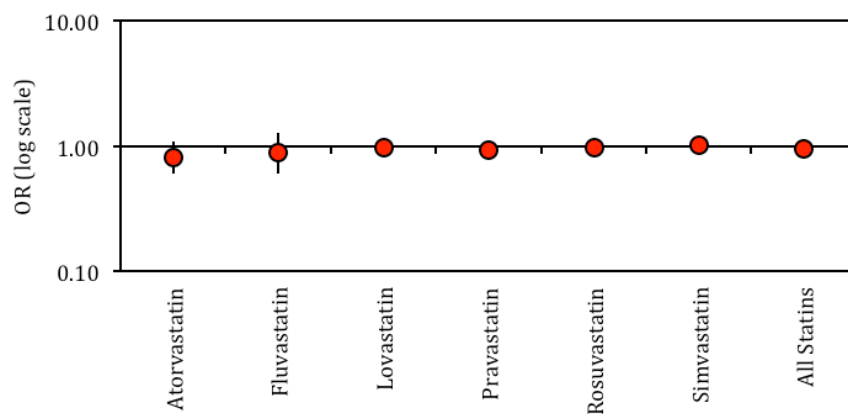
### 6.7.1 Cancer

#### 6.7.1.1 Harms of Statins vs. Control: Findings of the Traditional Pair-wise Meta-analysis

The pair-wise meta-analysis of placebo-controlled trials of statins included 5,514 individuals with incident cancers among 100,523 trial participants in 21 trials. There were two trials of atorvastatin providing information on 194 individuals with incident cancers among 5,280 participants; two trials of fluvastatin with 123 individuals with incident cancers among 1,996 trial participants; two trials of lovastatin with 522 individuals with incident cancers among 6,852 participants; 10 trials of pravastatin with 2,048 individuals with incident cancers among 38,516 participants; two trials of rosuvastatin with 773 individuals with incident cancers among 22,645 participants; and three trials of simvastatin providing information on 1,824 individuals with incident cancers among 25,234 trial participants.

Overall, as shown in Figure 6.28, statin therapy was not associated with a significant increase in the risk of incident cancers (OR: 0.96, 95% CI: 0.91, 1.02,  $I^2=0.0\%$ ). None of the individual statins appeared to significantly increase the risk of incident cancers as compared to control treatment in placebo-controlled trials: atorvastatin (OR: 0.81, 95% CI: 0.60, 1.80,  $I^2=0.0\%$ ); fluvastatin (OR: 0.89, 95% CI: 0.61, 1.28,  $I^2=0.0\%$ ); lovastatin (OR: 0.97, 95% CI: 0.82, 1.17,  $I^2=0.0\%$ ); pravastatin (OR: 0.94, 95% CI: 0.86, 1.03,  $I^2=0.0\%$ ); rosuvastatin (OR: 0.97, 95% CI: 0.84, 1.12,  $I^2=0.0\%$ ); and simvastatin (OR: 1.01, 95% CI: 0.92, 1.11,  $I^2=0.0\%$ ).

**Figure 6.28** – Effect of statins compared to control on the risk of incident cancers across all populations.\*



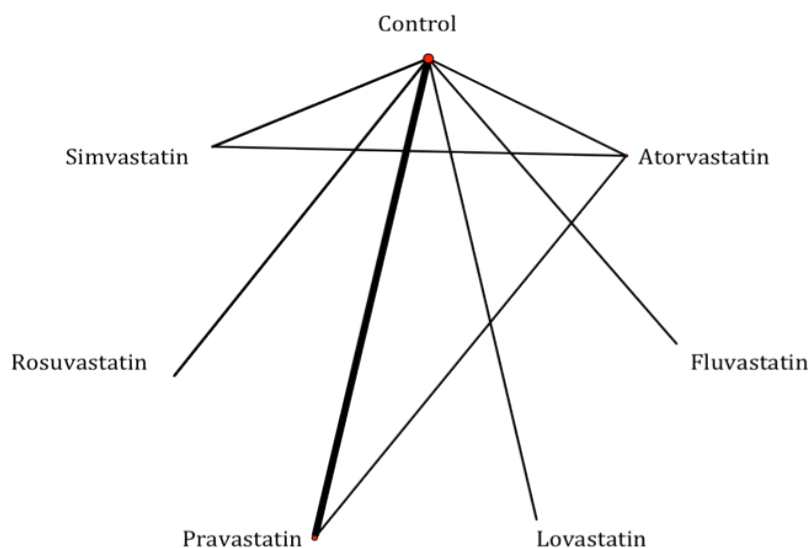
\* Estimates shown are ORs and 95% CIs.

### 6.7.1.2 *Comparative Harms of Individual Statins: Findings of the Network Meta-analysis*

The network of eligible comparisons is shown in Figure 6.29. In addition to the placebo-controlled trials included in the traditional pair-wise meta-analysis, the network meta-analysis included a total of four direct comparisons including 219 incident cancers among 11,520 trial participants. In total, there were 26 trials including 112,045 participants providing information on 5,733 incident cancers.

In the network meta-analysis, there were no statistically detectable differences among individual statins (Table 6.16).

**Figure 6.29** – Network of available comparisons for determining the comparative effects of individual statins on the risk of incident diabetes.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

**Table 6.16** – Comparative effects of individual statins on creatine kinase elevations across all populations.\*

	<b>Fluvastatin</b>	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	0.94 (0.59, 1.47)	0.86 (0.60, 1.2)	0.90 (0.69, 1.20)	0.84 (0.62, 1.16)	0.84 (0.66, 1.08)
<b>Fluvastatin vs.</b>	-	0.91 (0.58, 1.43)	0.97 (0.65, 1.45)	0.90 (0.58, 1.39)	0.90 (0.6, 1.37)
<b>Lovastatin vs.</b>	-	-	1.06 (0.81, 1.42)	0.99 (0.73, 1.36)	0.98 (0.75, 1.34)
<b>Pravastatin vs.</b>	-	-	-	0.94 (0.73, 1.19)	0.93 (0.77, 1.15)
<b>Rosuvastatin vs.</b>	-	-	-	-	0.99 (0.78, 1.30)

\* Estimates shown are ORs and 95% CrIs. Table should be read from left to right.

## 6.7.2 Diabetes

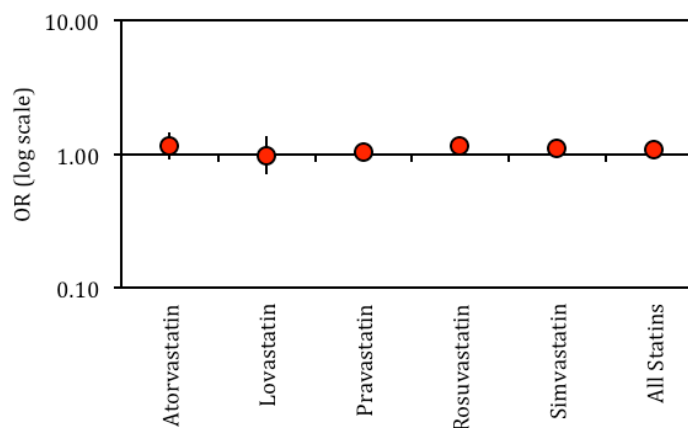
### 6.7.2.1 Harms of Statins vs. Control: Findings of the Traditional Pair-wise Meta-analysis

In the traditional pair-wise meta-analysis of statin therapy vs. control across all populations, 113,698 trial participants contributed information on 4,280 individuals with incident diabetes across 15 placebo-controlled trials. There was one trial of atorvastatin providing information on 288 individuals with incident diabetes among 10,305 participants; one trial of lovastatin providing information on 146 individuals with incident diabetes among 6,605 trial participants; seven trials of pravastatin with 1,712 incident diabetics among 44,444 trial participants; four trials of rosuvastatin providing information on 1,115 individuals with incident diabetes among 27,656 trial participants; two trials of simvastatin providing information on 1,019 individuals with incident diabetes among 24,980 trial participants.

Overall, as shown Figure 6.30, statin therapy was associated with an increase in the risk of incident diabetes (OR: 1.15, 95% CI: 0.91, 1.45,  $I^2=0.0\%$ ). Among individual statins, only rosuvastatin resulted in a statistically significant increase in the odds of incident diabetes as compared to control treatment (OR: 1.16, 95% CI: 1.02, 1.31,  $I^2=0.0\%$ ) (Figure 6.30). The remaining statins were not associated with an increase in the risk of incident diabetes: atorvastatin (OR: 1.15, 95% CI: 0.91, 1.45,  $I^2=0.0\%$ ); lovastatin (OR: 0.97, 95% CI: 0.70, 1.35,

$I^2=0.0\%$ ); pravastatin (OR: 1.03, 95% CI: 0.91, 1.17,  $I^2=37.1\%$ ); and simvastatin (OR: 1.10, 95% CI: 0.97, 1.25,  $I^2=0.0\%$ ).

**Figure 6.30** – Effect of statins compared to control on the risk of incident diabetes across all populations.\*

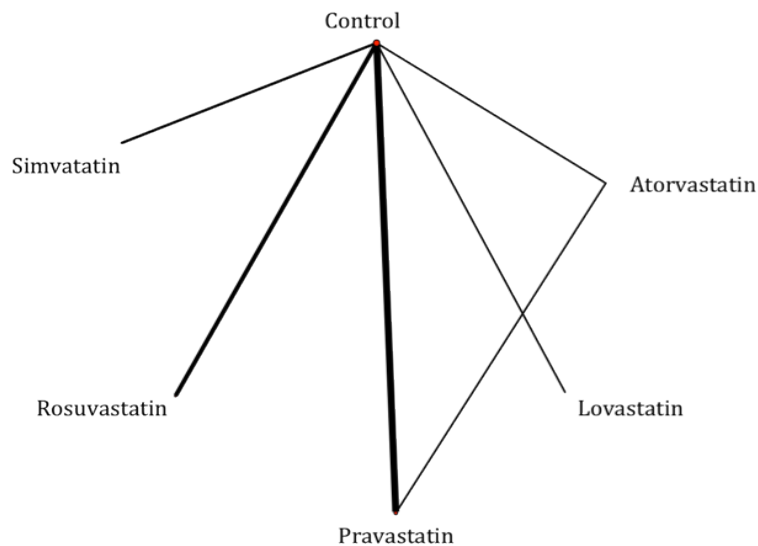


\* Estimates shown are ORs and 95% CIs.

#### 6.7.2.2 Comparative Harms of Individual Statins: Findings of the Network Meta-analysis

The network of eligible comparisons is shown in Figure 6.31. In addition to the placebo-controlled trials included in the traditional pair-wise meta-analysis, only one direct comparison was available, including 614 trial participants. In this trial, which provided information on a single individual with incident diabetes, atorvastatin was directly compared to pravastatin. The base-case network meta-analysis did not detect any statistical differences among individual statins in terms of increasing the risk of incident diabetes (Table 6.17).

**Figure 6.31** – Network of available comparisons for determining the comparative effects of individual statins on the risk of new-onset diabetes.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

**Table 6.17** – Comparative effects of individual statins on the risk of incident diabetes across all populations.\*

	<b>Lovastatin</b>	<b>Pravastatin</b>	<b>Rosuvastatin</b>	<b>Simvastatin</b>
<b>Atorvastatin vs.</b>	1.18 (0.71, 1.99)	1.12 (0.79, 1.62)	1.01 (0.69, 1.47)	1.06 (0.72, 1.57)
<b>Lovastatin vs.</b>	-	0.95 (0.62, 1.46)	0.85 (0.54, 1.33)	0.9 (0.56, 1.41)
<b>Pravastatin vs.</b>	-	-	0.90 (0.7, 1.12)	0.94 (0.72, 1.21)
<b>Rosuvastatin vs.</b>	-	-	-	1.05 (0.8, 1.4)

\* Estimates shown are ORs and 95% CrIs. There were no trials of fluvastatin reporting diabetes outcomes.

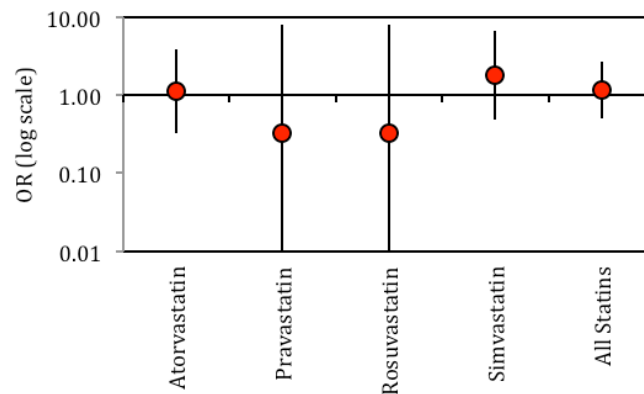
### 6.7.3 Rhabdomyolysis

#### 6.7.3.1 Harms of Statins vs. Control: Findings of the Traditional Pair-wise Meta-analysis

There were very few data points available for this analysis. In the traditional pair-wise meta-analysis of statin therapy vs. control across all populations, 60,605 participants contributed information on only 20 individuals with rhabdomyolysis events. There were four trials with nine events among 17,551 individuals; one trial of pravastatin with a single event among 326 individuals; one trial of rosuvastatin with one event among 17,802 trial participants; and two trials of simvastatin with nine events among 24,986 individuals.

As shown in Figure 6.32, statin therapy was not associated with a significant increase in the odds of rhabdomyolysis events as compared to control (OR: 1.17, 95% CI: 0.51, 2.72,  $I^2=0.0\%$ ). None of the individual statins resulted in statistically significantly higher odds of rhabdomyolysis as compared to control: atorvastatin (OR: 1.14, 95% CI: 0.33, 4.00,  $I^2=0.0\%$ ); pravastatin (OR: 0.33, 95% CI: 0.01, 8.19,  $I^2=0.0\%$ ); rosuvastatin (OR: 1.84, 95% CI: 0.50, 6.79,  $I^2=0.0\%$ ); and simvastatin (OR: 1.84, 95% CI: 0.50, 6.79,  $I^2=0.0\%$ ).

**Figure 6.32** – Effect of statins compared to control on the risk of rhabdomyolysis across all populations.\*



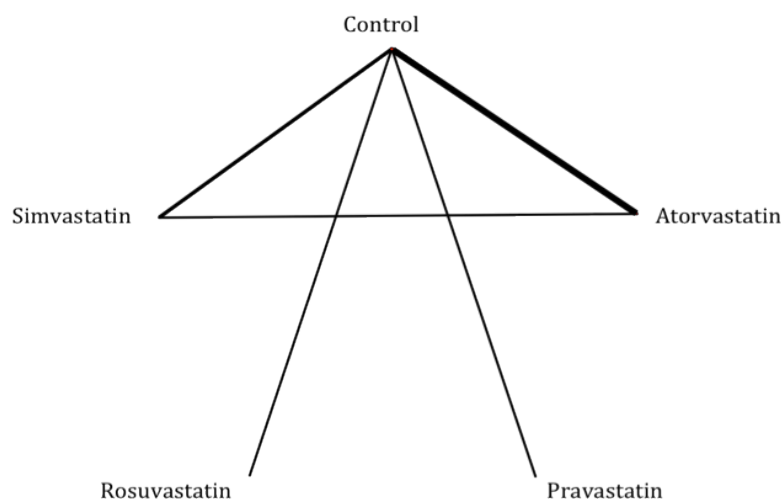
\* Estimates shown are ORs and 95% CIs. There were no trials of fluvastatin and lovastatin reporting rhabdomyolysis outcomes.

#### 6.7.3.2 Comparative Harms of Individual Statins: Findings of the Network Meta-analysis

The network of eligible comparisons is shown in Figure 6.33. In addition to the placebo-controlled trials included in the traditional pair-wise meta-analysis, there was one direct head-to-

head comparison between atorvastatin and simvastatin, which provided information on five individuals with rhabdomyolysis events. In total, nine trials including 69,493 participants were included in the base-case network meta-analysis, which provided information on 25 individuals who experienced rhabdomyolysis. However, this analysis failed to converge due to the extremely small numbers of events.

**Figure 6.33** – Network of available comparisons for determining the comparative effects of individual statins on rhabdomyolysis events.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

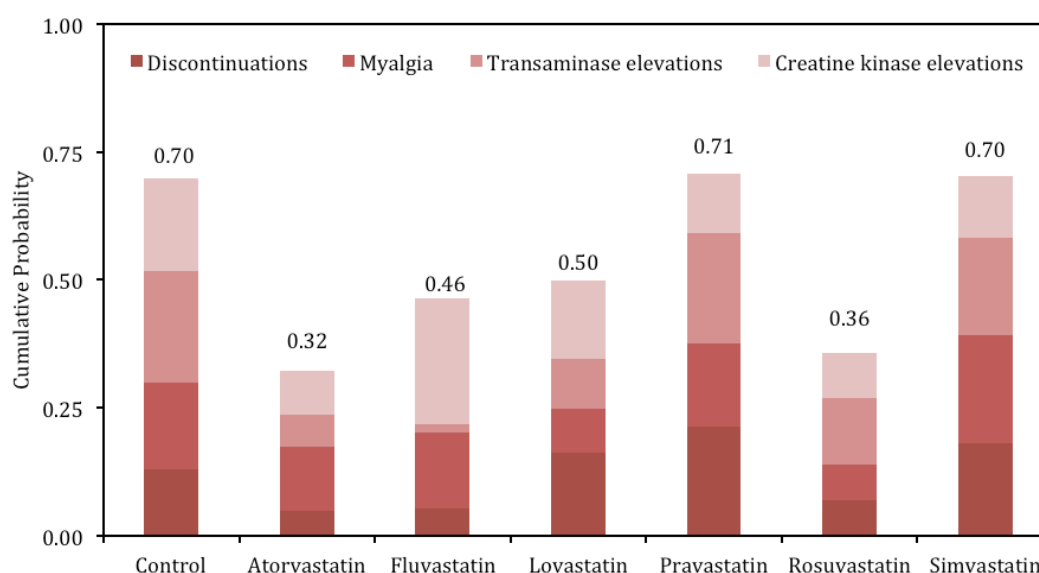
## 6.8 Overall Rankings of Individual Statins in Terms of Harm Outcomes Across All Populations

Network meta-analyses presented in this chapter detected a number of statistically significant differences among individual statins in terms of their comparative effects on discontinuations due to adverse events, myalgia, transaminase elevations, and creatine kinase elevations. In addition to statistically detectable differences, the magnitude of comparative effects as well as their uncertainty varied considerably.

Combining the results of the network meta-analyses on the outcomes with the most abundant data (trial discontinuations due to adverse events [tolerability], myalgia occurrence, transaminase elevations, and creatine kinase elevations), the overall rankings for the individual

statins are shown in Figure 6.34. In addition to the overall score for each statin, the relative contribution of each outcome (discontinuations, myalgia, transaminase, and creatine kinase elevations) to the overall score is also shown. Pravastatin ranked first with an overall score of 0.71 out of 1.00, followed by simvastatin (0.70), and lovastatin (0.50), suggesting that these statins had the most favorable tolerability and harm profile on the basis of discontinuations due to adverse events, myalgia, transaminase elevations, and creatine kinase elevations (Figure 6.34). As expected, control treatment ranked very favorably with a total score of 0.70 out of 1.00.

**Figure 6.34** – Ranking of individual statins on the basis of discontinuations due to adverse events, myalgia, transaminase elevations, and creatine kinase elevations.



## 6.9 Summary of Findings

This network meta-analysis of 233,783 participants provided comprehensive evidence on the comparative tolerability and harms of individual statins using both placebo-controlled and active-comparator trials. Overall, statins as a class were associated with an increased risk of diabetes and hepatic transaminase elevations with no statistically detectable effect on myalgia, myopathy, rhabdomyolysis, and cancer. Across the totality of the evidence base, higher doses of some statins resulted in higher odds of experiencing discontinuations due to adverse events, transaminase elevations and creatine elevations. When compared head-to-head in network meta-analyses, there were differences among individual statins, with pravastatin and simvastatin likely to be ranked superior to their alternatives in terms of their safety profile.

The findings of the empirical work presented in this chapter contribute to two ongoing debates about the effect of statins on diabetes and cancer incidence. First, this review and meta-analysis confirmed the findings of previous pair-wise meta-analyses in that statins as a class are associated with higher odds of developing diabetes<sup>368</sup> Interestingly, rosuvastatin remains the only statin that has an independent association with an increased risk in incident diabetes among individual statins. While the findings of network meta-analyses cannot distinguish between rosuvastatin and other statins in terms of their effects on new onset diabetes due to generally wide credible intervals around relative treatment effects, this should be the focus of future prospective studies.

Another widely disputed issue relates to whether statins cause or prevent cancer.<sup>393-396</sup> Duncan and colleagues hypothesized that statins may be able to promote the growth of cancer cells due to their effect on the HMG-CoA reductase metabolism.<sup>397</sup> However, almost unequivocal evidence from randomized and non-randomized studies suggested that statins either do not have an effect on cancer incidence or may be protective against certain types of cancers.<sup>385-387,398-404</sup> The findings of the review and meta-analysis presented in this chapter confirmed the lack of evidence that statins are associated with an increased risk of developing cancers. These findings may even suggest that atorvastatin is protective against cancer (although not statistically significant).

A challenging issue for prescribers is the association of statin use with elevations in liver enzymes. This review confirmed that statins are associated with clinically meaningful elevations in hepatic transaminase concentrations.<sup>405</sup> These are asymptomatic and (mostly) reversible elevations in liver enzymes called transaminases, which may be indicative of liver toxicity if they reach very high levels. Although drug-induced hepatic toxicity is possible among some patients (as with any drug), this risk is extremely low with statins. Prescribers routinely evaluate hepatic transaminases (and other enzymes such as creatine kinase) in individuals who may be at risk of experiencing such elevations. The findings presented in this chapter provide further assistance to prescribers in selecting the statins that are associated with lower odds of hepatic transaminase elevations.

Although this review did not find statistical evidence of myalgia, this may be due to an under-detection of muscle toxicity and its associated muscle aches in clinical trials.<sup>406-408</sup> Similar to previous reviews of randomized controlled trials, the frequency of these adverse events in the randomized controlled trial literature is extremely low. However, the occurrence of myalgia in actual clinical practice remains a common side effect associated with the use of statins.

An important motivation for undertaking this empirical work was that available statins differ to a various extent in pharmacological properties and it would be expected that they differ in terms of their side effects.<sup>87,104</sup> Nonetheless, their comparative harms had not been evaluated in a comprehensive manner in previous reviews. The findings of the review and meta-analysis presented this chapter showed that there are statistically detectable differences between individual statins in terms of their tolerability and harms: across populations, differences were observed in discontinuations due to adverse events, hepatic transaminase elevations, and creatine kinase elevations. At the drug-level, individuals receiving simvastatin and pravastatin appeared to have the lowest odds of experiencing discontinuations due to adverse events, myalgia, and transaminase and creatine kinase elevations. These findings were not influenced by study-level characteristics, which were evaluated in the meta-regression analyses. Specifically, baseline mean age, LDL cholesterol concentration, and trial publication year did not have an impact on the observed findings.

Among individuals with established coronary heart disease (secondary prevention population), atorvastatin was more likely to result in hepatic enzyme elevations as compared to pravastatin and simvastatin; fluvastatin led to more transaminase elevations than pravastatin and simvastatin. Generally, similar trends were apparent in the primary prevention population; however, these findings were associated with considerable uncertainty due to the smaller number of data points available for the analysis. Unfortunately, there were no trials of fluvastatin among individuals without established coronary heart disease.

The dose-specific analysis paralleled the findings of previous meta-analyses in that more intensive statin therapy is associated with greater risk of harm and less favorable tolerability as compared to lower doses.<sup>382,409-411</sup> Similar to previous studies, there was a weak dose-response relationship across placebo-controlled and active-comparator trials in terms of discontinuations due to adverse events, transaminase elevations, and creatine kinase elevations.

The findings of this comparative analysis should be interpreted in light of its limitations. First, the randomized controlled trials of statins included in this review did not report acute kidney failure, which is a rare but important harmful side effect associated with statin therapy. Recent observational analyses evaluated the effects of statins on this outcome.<sup>380</sup> Second, although there was no evidence of small-study effects, there was an apparent asymmetry in the evidence network where specific interventions seemed to be avoided (eg, fluvastatin). For instance, the relative effect of fluvastatin on creatine kinase elevations was estimated on the basis of only eight events observed in four trials. Similarly, there were only four trials of fluvastatin, which

reported hepatic transaminase elevations. Third, there was considerable heterogeneity across various traditional pairwise meta-analyses of statins versus control, particularly for hepatic transaminase elevations. It remains a possibility that the analyses did not fully account for heterogeneity as a result of unobserved or unmeasured factors. However, the random-effects model took into account potential unexplained heterogeneity across the studies. Also, meta-regression analyses further evaluated heterogeneity and inconsistency and did not detect a significant effect of study-level covariates such as baseline mean LDL cholesterol concentrations, publication year, and baseline mean age of patients.

Despite these limitations, the empirical work presented in this chapter has important methodological strengths. First, this review is the largest meta-analysis on the harms of statin therapy to date, including almost a quarter-million trial participants. Second, this review incorporated data from a comprehensive list of trials, irrespective of placebo or active controls, including all clinically used statins. In total, there were 78 active-comparator trials with or without a placebo or usual care arm. Third, the empirical work in this chapter evaluated the dose-comparative harms of individual statins.

#### *6.9.1 Clinical Implications*

The findings of this empirical chapter have clinical implications. First, there is strong evidence that statins as a class are generally safe with uncommon side effects. According to the findings of this comprehensive analysis, there is consistently strong evidence on the comparatively favorable side effect profile of simvastatin and pravastatin – particularly at low to moderate doses – which should be taken into account in prescribing decisions. Finally, this meta-analysis sheds new light on the clinical discussion on the relation between statins and diabetes incidence and confirms that statin use is not associated with cancer incidence.

## Chapter 7

### Methodological Quality and Risk of Industry Sponsorship Bias in the Randomized Controlled Trials of Statins\*

Over the past 25 years, large placebo-controlled trials of statins informed influential clinical practice guidelines, which in turn progressively expanded the limits of statin therapy to populations at lower risk of developing cardiovascular disease. In addition to placebo-controlled trials, a large number of head-to-head randomized controlled trials evaluated the dose-comparative effects of individual statins, and established some statins as more efficacious than others. Network meta-analyses presented in Chapters 4-6 of this thesis combined the findings of these placebo-controlled and active-comparator trials of statins to examine their comparative benefit and harm profiles to inform future prescribing decisions. The findings of such comparative assessments can be jeopardized due to potential bias in the randomized controlled trials of individual statins. Of particular concern are bias that can be attributed to (1) flaws in the methodological quality of trials and (2) industry sponsorship. If present, bias can render the findings of comparative analyses invalid. Therefore, this chapter evaluates the methodological quality and risk of industry sponsorship bias in the randomized controlled trials of statins.

#### 7.1 Methodological Quality

The fact that the comprehensive meta-analyses presented in the previous chapters were based on randomized controlled trials has significant implications for the credibility of their findings. Randomized controlled trial designs are considered the gold standard for determining whether a health intervention works or is more effective than another treatment. As discussed in Chapter 3 (*Evidence Review and Synthesis Methods*), such designs have high internal validity, i.e., can

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\* Part of the contents of this chapter is currently under review with the following reference: Naci H, Dias S, Ades AE. Industry sponsorship bias in research findings: A network meta-analytic exploration of the randomized controlled trials of statins. Under Review.

ensure that the observed treatment effect can be attributed to the experimental treatment. The internal validity of randomized controlled trials is achieved by two key design features.<sup>412,413</sup> First, by randomly allocating patients to treatment groups, researchers can ensure that there are no systematic differences in patient groups at baseline in terms of known (and unknown) factors that may influence outcomes. Second, by carefully establishing a controlled environment where patients receive care, researchers ensure that there are no systematic differences between treatment groups in terms of how they receive treatment and are followed up.

Although typically placed at the top of evidence hierarchies,<sup>414</sup> causal inferences from randomized trials can be jeopardized by limitations in methodological quality in their design, conduct, analysis, and reporting, leading to underestimation or overestimation of the true intervention effect, i.e., bias.<sup>415-419</sup> In 1995, a seminal quantitative study by Schulz and colleagues showed that inadequate methodological approaches in randomized trials were associated with systematically different (and often exaggerated) treatment effects.<sup>420</sup> In particular, this study provided empirical evidence on the association between four dimensions of methodological quality (allocation concealment, sequence generation, blinding, and incomplete data) and the magnitude of treatment effects. In later years, other studies provided empirical evidence on the association between treatment effects and sequence generation,<sup>421</sup> allocation concealment,<sup>422</sup> blinding of participants and personnel,<sup>422</sup> blinding of outcome assessment,<sup>422</sup> selective reporting of outcomes,<sup>423</sup> incomplete outcome data,<sup>424</sup> and selective outcome reporting.<sup>425-427</sup>

Consistent with the empirical findings of this body of literature evaluating the methodological biases in randomized controlled trials, the Cochrane Collaboration recently categorized the potential biases in randomized controlled trials as selection bias, performance bias, attrition bias, detection bias and reporting bias.<sup>428</sup> These biases are outlined in Table 7.1 along with methodological approaches to prevent them.

In recent meta-epidemiological studies (i.e., meta-analyses of meta-analyses), blinding of trial participants and personnel was shown to have the strongest effect on observed study outcomes in randomized controlled trials, followed by allocation concealment.<sup>429</sup> However, the average bias associated with limitations in the methodological quality of randomized trials appeared to vary with the type of outcome: there was no statistically detectable bias for objective outcomes such as all-cause mortality and laboratory measures. In the largest meta-epidemiologic study to date, Savovic and colleagues found that lack of, or unclear double-blinding (vs. double-blinding), was associated with an average of 13% exaggeration of treatment effects, which was also driven primarily by trials with subjective outcomes.<sup>430</sup> However, there was no evidence that other

methodological quality attributes were associated with systematic discrepancies in study outcomes – particularly for objective outcomes.

**Table 7.1** – Categorization of potential biases in randomized controlled trials.\*

<b>Bias domain</b>	<b>Definition</b>	<b>Methodological approach to prevent bias</b>
<i>Selection bias</i>	Systematic differences between characteristics of the treatment groups that are compared in a given trial	<ul style="list-style-type: none"> <li>• Random sequence generation</li> <li>• Allocation concealment</li> </ul>
<i>Performance bias</i>	Systematic differences between groups in care provided	<ul style="list-style-type: none"> <li>• Blinding of personnel and participants</li> </ul>
<i>Detection bias</i>	Systematic differences between groups in how outcomes are determined	<ul style="list-style-type: none"> <li>• Blinding of outcome assessment</li> </ul>
<i>Attrition bias</i>	Systematic differences between groups in withdrawals from a study, resulting in incomplete outcome data	<ul style="list-style-type: none"> <li>• Properly dealing with incomplete data (e.g., conduct intention-to-treat analysis, ensure balance of withdrawals in treatment groups, impute data using appropriate techniques, ensure missing data are not associated with true outcome)</li> </ul>
<i>Reporting bias</i>	Systematic differences between reported and unreported findings	<ul style="list-style-type: none"> <li>• Reporting findings on all pre-specified outcomes</li> </ul>

\* Adapted from the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.<sup>415</sup>

In addition to potential biases within trials, an added risk of bias in a network meta-analysis is that limitations in the design, conduct, analysis, and reporting of randomized trials may differ across different comparisons within the evidence network.<sup>307</sup> Therefore, a meaningful evaluation of the methodological quality would need to examine the distribution of methodological quality across the entire evidence network. In the case of the statin network meta-analysis presented in this thesis, it is difficult to speculate whether the risk of bias due to methodological quality attributes influence some statins more than others, which would have implications for the observed comparative effectiveness and safety of individual statins. Accordingly, examining the distribution of methodological quality attributes in the statin evidence network is the first objective of this chapter.

## 7.2 Industry Sponsorship

Another potential cause of bias relates to the influence of pharmaceutical industry sponsorship on the study findings. A growing share of biomedical research in the United States is sponsored

by industry,<sup>431</sup> and findings from industry-sponsored research are increasingly the most influential, i.e., the most frequently cited.<sup>432</sup> There are clear financial conflicts of interest with pharmaceutical company sponsorship of randomized controlled trials. Unsurprisingly, pharmaceutical companies may not wish to risk unfavorable trial results, which would have significant financial implications. Irrespective of financial interests, academic investigators may be willing to be funded by the industry to advance their professional recognition and become “key opinion leaders” (or “thought leaders”) for pharmaceutical companies.<sup>433</sup> Over time, industry sponsorship may influence researchers’ attitudes and habits of thought towards the pharmaceutical industry and its products – potentially jeopardizing the validity of findings obtained from industry-sponsored randomized trials.<sup>434</sup>

The question of whether the conflicts of interest that intertwine industry sponsors and investigators influence the outcome of randomized trials is of great academic interest. Three comprehensive (and influential<sup>§§§</sup>) studies conducted over the past decade provided evidence that research sponsored by the pharmaceutical industry is more likely to favor the product developed by the company sponsoring the research than research funded by other sources.

First, Bekelman and colleagues systematically documented the nature and influence of financial conflicts of interest in biomedical research.<sup>435</sup> Reviewing quantitative studies on the extent and impact of financial conflicts of interest, Bekelman and colleagues showed that studies that compared the outcome of industry-sponsored vs. nonindustry-sponsored studies were over three times more likely to report favorable results for the sponsored product (OR: 3.60, 95% CI: 2.63, 4.91). When they stratified their results and focused specifically on randomized controlled trials (as opposed to including other study types such as economic evaluation analyses), studies funded by the industry had over four times the odds of yielding pro-industry conclusions (OR: 4.14, 95% CI: 2.72, 6.32).

Second, Lexchin and colleagues performed another study to examine the link between pharmaceutical industry sponsorship and research outcome.<sup>436</sup> Across a broad range of therapeutic conditions, patient populations, and outcomes, this analysis included sixteen reviews that investigated the relationship between funding source and the outcomes of clinical trials and meta-analyses. Studies sponsored by pharmaceutical companies were more likely to have outcomes favoring the sponsor than were studies with other sponsors (OR: 4.05, 95% CI:

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<sup>§§§</sup> At the time of writing this thesis, these landmark analyses evaluating the presence of industry sponsorship bias in randomized controlled trials were collectively cited over 2,500 times.

2.98, 5.51), which led the authors to conclude: “there is some kind of systematic bias to the outcome of published research funded by the pharmaceutical industry.”<sup>436</sup>

Third, a recent systematic review by the Cochrane Collaboration appeared to corroborate the findings of previous reviews.<sup>437</sup> This review showed that the number of studies with favorable results was higher among industry-sponsored studies compared with nonindustry-sponsored studies (RR: 1.24, 95% CI: 1.14, 1.35).<sup>438</sup> Similarly, the reports of industry-sponsored studies presented more favorable overall conclusions compared with nonindustry-sponsored studies (RR: 1.31, 95% CI: 1.20, 1.44). In industry-sponsored head-to-head comparisons, the drug that compared favorably was most often the drug manufactured by the study sponsor.

In 2007, Bero and colleagues published an analysis examining the association between industry sponsorship, study design characteristics, and reported conclusions in head-to-head comparisons of individual statins and other drugs.<sup>439</sup> Consistent with the findings of previous analyses on industry sponsorship bias, Bero and colleagues – aptly titled: *Why Some Statins Appear More Efficacious than Others* – showed that head-to-head comparisons of statins and other drugs were more likely to report results and conclusions favoring the sponsor's product compared to the comparator drug, suggesting the presence of industry sponsorship bias. These findings led the authors to conclude: “This bias in drug–drug comparison trials should be considered when making decisions regarding drug choice.”<sup>439</sup>

There are two potential explanations for the observed relationship between industry sponsorship and research outcome. These explanations, if supported empirically, would offer alternative (yet potentially complementary) mechanisms of industry sponsorship bias in clinical research. The first suggests that pharmaceutical companies introduce bias into individual randomized controlled trials, rendering their findings invalid. Indeed, it was originally hypothesized that pharmaceutical companies conducted poor quality research, resulting in findings that favored their own products. However, there is now conclusive evidence from systematic reviews that the methodological quality of industry-sponsored studies is at least as good as (and sometimes better than) those of nonindustry-funded studies.<sup>435,436,440</sup> Using a comprehensive list of studies, the recent Cochrane Collaboration review confirmed that there is generally no difference between industry and nonindustry-sponsored studies in methodological quality that may increase the risk of bias, such as randomization sequence, allocation concealment, and follow-up. To the contrary, industry sponsored studies generally report adequate blinding more often than nonindustry-sponsored studies.<sup>438</sup>

The second oft-cited potential explanation for the observed link between industry sponsorship and exaggerated research outcomes refers to what is commonly termed “design bias”, i.e., limitations in the planning and design considerations preceding the conduct, analysis, and reporting of trials.<sup>434</sup> For example, Lexchin and colleagues suggested that pharmaceutical companies may ask the “right” questions and preferentially sponsor trials on a drug that they consider to be superior to its alternatives.<sup>436</sup> In a similar fashion, industry may selectively design trials that favor positive results, such as the use of placebo comparisons.<sup>434</sup> As an extension of this potential design bias, in head-to-head trials, industry sponsors may exclusively compare their products to active treatments known to be inferior, or use too low a dose of a competitor drug, deliberately reducing its observed efficacy.<sup>441,442</sup> Although the findings of industry-sponsored trials with ‘straw-man comparators’ may still have high internal validity, such design biases would distort the evidence base in favor of industry-sponsored products.

While these explanations are plausible, and consistent with anecdotal evidence put forth in recent popular books on the pharmaceutical industry,<sup>433,443-446</sup> studies in the scholarly literature provided limited empirical evidence supporting these hypotheses. First, the previous finding that industry-sponsored trials have high methodological quality does not necessarily mean that companies do not bias individual trials through their influence on other domains not covered by traditional risk of bias assessments. Empirical evidence for an industry sponsorship bias would show that industry-sponsored trials produce systematically exaggerated findings compared to those obtained from *identical* (or at least comparable) trials funded by nonindustry sources.<sup>447</sup> However, such comparability has rarely been established in previous studies: the existing body of literature did not take into account the important differences across industry- and nonindustry-sponsored studies. These include actual differences in drug interventions, patient populations, and dosing regimens, which collectively influence the observed treatment effects in randomized trials. In addition, previous analyses demonstrated a statistical association between industry sponsorship and trial conclusions, rather than differences in the *magnitude* of effect sizes between industry- and nonindustry-sponsored trials.<sup>448</sup> Therefore, previous comprehensive analyses did not provide sufficient evidence either for or against the presence of industry sponsorship bias in individual randomized controlled trials.

For a collective set of trials, there is also limited empirical evidence for the presence of design bias. Currently, it is not clear by which mechanism design bias would operate, and how it would influence a complex evidence network including a large number of placebo-controlled and active-comparator trials. One possibility is that the share of randomized trials with placebo comparisons is higher among industry-sponsored trials as compared to trials funded by

nonindustry sources. In a systematic analysis of the clinical trial registry ClinicalTrials.gov, Lathyris and colleagues showed that the large majority of industry-sponsored trials was placebo-controlled and examined a single drug owned by the sponsoring company.<sup>449</sup> However, whether a similar majority of nonindustry-sponsored trials was placebo-controlled is not known. Another way to conceive of design bias is that industry-sponsored trials include (drug and dose) comparisons that are almost exclusively different than those included in nonindustry-sponsored trials. For example, Heres and colleagues showed that industry sponsors selectively used suboptimal comparators in the trials of antipsychotics.<sup>450</sup> While acknowledging the challenges associated with choosing dosing schedules for antipsychotic agents, Heres and colleagues suggested that pharmaceutical companies did not always use the appropriate dose range and titration schedule for their competitors' products in head-to-head comparisons, primarily because in numerous trials dose ranges were determined according to the manufacturer's package insert, which often did not reflect the latest state of knowledge about proper dosing. Whether similar 'straw-man' comparators were used in nonindustry-sponsored trials is not known.

Taken together, although the existing body of literature on industry sponsorship bias provides seemingly unequivocal evidence for the exaggeration of results (favoring sponsoring company's product) in industry-sponsored trials, it is not clear whether (or to what extent) industry involvement in the randomized trials of statins affected the findings of the empirical analyses presented in Chapters 4-6 of this thesis. The objective of this chapter was to explore the methodological quality and risk of industry sponsorship bias in a systematically identified set of placebo-controlled and active-comparator trials of statins.

### **7.3 Empirical Considerations**

As outlined in Chapter 3 (*Evidence Review and Synthesis Methods*), a network meta-analytic approach was used to examine the methodological quality and risk of industry sponsorship bias in the randomized trials of statins. By taking into account actual differences in the effectiveness of individual statins at different doses, network meta-analysis provided an analytic framework for the exploration of bias.<sup>451</sup> The network analyses presented in this chapter pooled all primary and secondary prevention trials in addition to trials with mixed patient populations, including all placebo-controlled and active-comparator trials eligible for inclusion in the systematic review.

The primary outcome of interest was the mean change from baseline in serum LDL cholesterol levels between two comparator treatments for a given dose (change from baseline in the

treatment group minus that in the control group). Accordingly, both the methodological quality and risk of bias were evaluated on the basis of the mean change from baseline in serum LDL cholesterol levels. Mean LDL cholesterol reduction from baseline was the most frequently reported outcome in the randomized controlled trials of statins. Another important advantage of using this outcome was its objective nature. As previous meta-epidemiological studies have shown, objective outcomes such as laboratory assessments are largely immune to biases resulting from methodological quality deficits in trials.<sup>429,430</sup>

Consistent with the network meta-analyses presented in Chapter 4 (*Dose-Comparative Effects of Individual Statins on Cholesterol Concentrations*), all analyses were dose-specific and explored the effects of individual statins at different doses separately. Each statin-dose combination was considered as a different treatment and no trends were fitted or assumed. All analyses were based on the total number of randomly assigned participants regardless of how the study authors analysed the data.

*Definition of bias:* Two sources of bias were explored. First was quality-related bias, which was defined as the potential underestimation or overestimation of the true intervention effect due to flaws in the methodological attributes of randomized controlled trials.<sup>415</sup> Second, industry sponsorship bias, which could occur when a pharmaceutical company sponsor favors its own drug in placebo-controlled or active-comparator trials, or the highest dose of its own drug in dose-comparator trials, was explored.<sup>451</sup>

As described previously in Chapter 3 (*Evidence Review and Synthesis Methods*) six attributes of methodological quality were considered in the evidence review conducted for this thesis.<sup>415</sup> These were blinding (i.e., did the investigators blind trial participants and researchers from knowledge of which treatment a trial participant received?); random sequence generation (i.e., were the methods for allocation sequence reported to determine whether it produced comparable groups?); allocation concealment (i.e., were the methods used to conceal the allocation sequence reported to determine whether group allocations could have been foreseen before or during treatment initiation?); blinding of outcome assessment (i.e., did trial investigators blind outcome assessment from knowledge of which intervention a participant received?); indications of incomplete outcome data (i.e., did the investigators report completeness of outcome data for LDL cholesterol lowering, including attrition and exclusions from the analysis?); and indications of selective reporting (i.e., did the investigators fail to report tolerability and harm outcomes commonly reported in randomized trials of statins [e.g.,

withdrawals due to adverse events, creatine kinase elevations, hepatic transaminase elevations, or myalgia]? Also, were there deviations in trial outcomes from published protocols?).

On each methodological attribute, each study was given a rating of high, low, or uncertain quality. For each trial, one point was assigned for each item with “high quality” to calculate the overall methodological quality score ranging from 0 (worst methodological quality) to 6 (best methodological quality). Trials did not receive any points for methodological attributes with “low quality” or “uncertain quality.” Using this information, the distribution of methodological quality of different comparisons across the evidence network was evaluated (e.g., explored whether trials comparing simvastatin vs. control had on average a higher or lower methodological quality score than those comparing atorvastatin vs. rosuvastatin).

*Mechanism of bias:* For the exploration of industry sponsorship bias, one statin (at a specific dose) per trial was coded as “potentially biased.” Two *a priori* hypotheses were considered for this designation by which industry sponsorship bias could occur in individual randomized trials (scenarios 1 and 2). The first (scenario 1) was that a pharmaceutical sponsor would favor its own drug in placebo-controlled or active-comparator trials of statins or the highest dose of its own drug if different doses were being considered.<sup>452</sup> Accordingly, one arm per trial was labeled as potentially biased in the industry-sponsored trials of statins. In scenario 2, the hypothesis was that a sponsor would favor its own drug in placebo-controlled or active-comparator trials of statins, but that it would neither differentiate between different doses of its own drug nor differentiate between its older and newer products. Accordingly, one arm per trial was labeled as potentially biased in the industry-sponsored trials of statins unless a given trial compared the same statin at different doses.

To explore the presence of design bias, the percentage of industry-sponsored trials with placebo controls was compared to the corresponding percentage in nonindustry-sponsored trials. In addition, the type of drug and dose comparisons was contrasted between industry- and nonindustry-sponsored trials.

As mentioned in Chapter 3 (*Evidence Review and Synthesis Methods*), in cases where trial funding source was not clearly reported, studies with industry-affiliated authors were categorized as industry-sponsored. Also, trials with industry, government, and/or academic institution co-sponsorship were categorized as industry-sponsored unless the trial investigators included a statement suggesting that the funding body had no involvement in trial design, conduct, analysis or reporting (seven of the industry-sponsored trials included a statement indicating that study sponsors did not have any involvement in the trial design, conduct, analysis, and reporting;

these trials were labeled as nonindustry-sponsored for the evaluation of industry sponsorship bias and they were labeled as industry-sponsored for the evaluation of design bias).

*Assessment of methodological quality:* To evaluate the sensitivity of base-case network meta-analysis findings on study-level methodological quality attributes, six sets of separate analyses were conducted, excluding studies with low quality on the following methodological items: (1) blinding of personnel and participants, (2) random sequence generation, (3) allocation concealment, (4) blinding of outcome assessment, (5) indications of incomplete outcome data, and (6) indications of selective reporting.

*Statistical exploration of industry sponsorship bias:* Industry sponsorship bias was first qualitatively evaluated by comparing the dose-comparative effects of individual statins obtained from an analysis including only industry-sponsored trials vs. those obtained from an analysis including only nonindustry-sponsored trials. The consistency of the relative treatment effects obtained from the two sets of analyses were visually inspected for potential differences. As described in Chapter 3, meta-regression analyses were subsequently conducted to statistically evaluate potential industry sponsorship bias.<sup>452-454</sup> Meta-regression analyses were performed by allowing for a common treatment-bias interaction for each statin-dose compared to control.<sup>327</sup> In addition to assuming that each trial estimated a study-specific bias, which came from a common bias distribution (i.e., random-effects model for bias), a separate analysis assumed that all studies estimated the same bias parameter (i.e., fixed-effect model for bias).

*Goodness of fit:* The relative goodness of fit of fixed-effect and random-effects models for bias was formally evaluated using the total residual deviance (posterior mean of the deviance under a given model minus the deviance for the saturated model) along with the deviance information criterion (sum of the posterior mean of the residual deviance and the effective number of parameters), as described in Chapter 3.<sup>320</sup> Due to better fit, only the results obtained from the fixed-effect model for bias were reported (total residual deviance for the fixed-effect model was 228.20 as compared to 229.20 for the random-effects model).

*Presentation of results:* First, the methodological quality of randomized controlled trials of statins was presented along with the distribution of methodological quality scores across the evidence network. The findings of separate sensitivity analyses excluding trials with low quality on various methodological quality attributes were then presented side-by-side with the base-case analysis, which included all eligible trials. After a qualitative description of potential design bias in the statin evidence base, dose-comparative effects obtained from industry-sponsored

trials were plotted together with treatment effects obtained from nonindustry-sponsored trials to visually inspect the magnitude of potential discrepancy between two sets of results.

*Interpretation of results:* Given the Bayesian nature of network meta-analyses, the findings of the statistical analyses were presented as mean changes from baseline and 95% CrIs. As previously, if a 95% CrI did not include the null value 0.00, this was interpreted as indicating <5% probability that there was no difference between the two comparisons. For the exploration of industry sponsorship bias, a negative meta-regression coefficient indicated the presence of industry sponsorship bias. The findings were considered 'statistically significant' if 95% CrIs excluded the null value 0.00.

#### **7.4 Systematic Review Findings**

There were 183 randomized controlled trials included in the systematic review and network meta-analysis of mean change from baseline LDL cholesterol levels (Figure 7.1). There were 54 trials conducted among individuals with established coronary heart disease; 42 trials were in primary prevention (nine of which were among individuals with diabetes); 11 included patients with acute coronary syndrome; four included patients with metabolic syndrome; and three were among patients with heart failure. The remaining 69 trials included individuals with hypercholesterolemia with or without established coronary heart disease.

**Figure 7.1** – Flow diagram of study identification and selection.

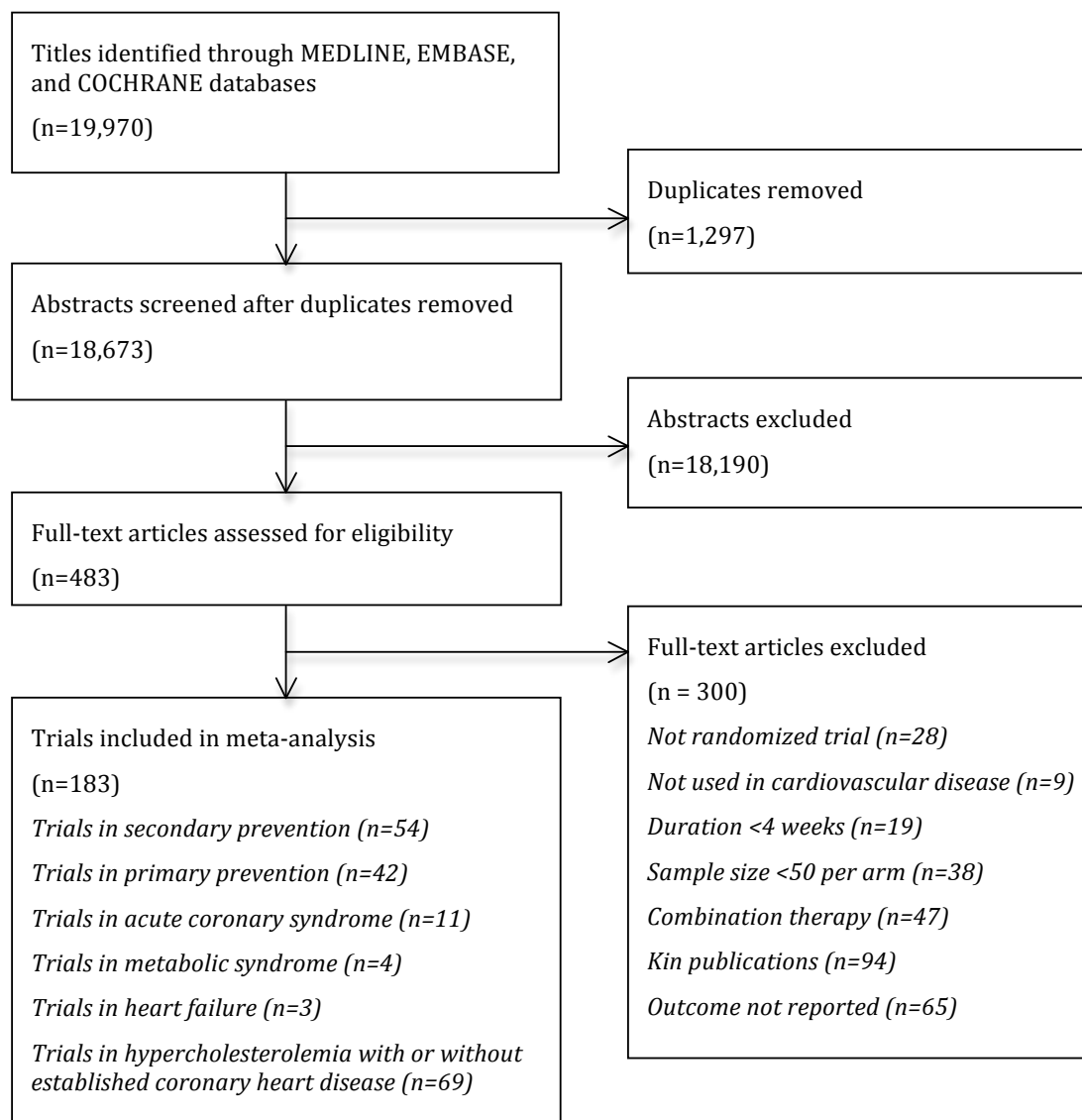
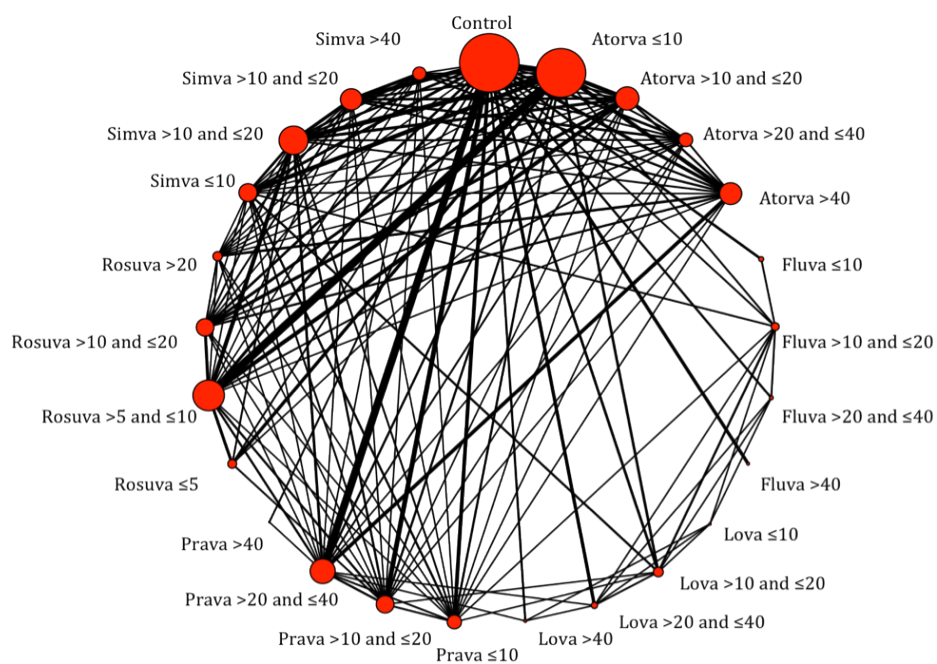


Figure 7.2 shows the network of eligible pair-wise comparisons for LDL cholesterol reductions from baseline in placebo-controlled and active-comparator trials of individuals across all populations. As outlined previously in Chapter 4 (*Dose-Comparative Effects of Individual Statins on Cholesterol Concentrations*), of the 15 possible pair-wise comparisons between the six statins, 11 were available in the identified literature. No trial directly compared all statin-dose combinations to each other. The majority of eligible trials included active comparators: there were 83 two-armed placebo-controlled trials as compared to 100 two- or multi-armed active-comparator trials. The frequency of comparisons varied widely across the evidence network. Most frequent comparisons occurred between pravastatin and placebo (n=34), rosuvastatin and atorvastatin (n=34), simvastatin and placebo (n=24), and atorvastatin and placebo (n=23). There were no comparisons between fluvastatin and rosuvastatin, and lovastatin and rosuvastatin at any dose formulation.

**Figure 7.2** – Network of available comparisons for determining the dose-comparative effects of individual statins on LDL cholesterol levels.\*



\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin.

## 7.5 Methodological Quality of Randomized Controlled Trials of Statins

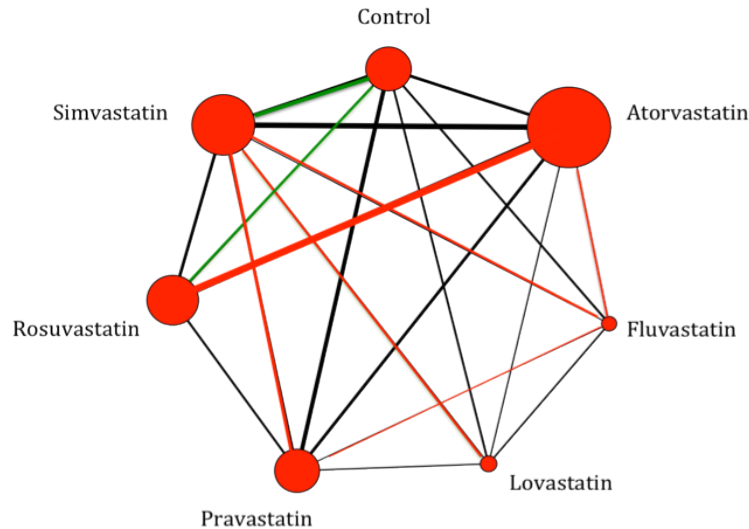
Out of a total of 183 randomized controlled trials included in this network meta-analysis, 112 were double-blind (rated as high quality) while 58 were open-label and two were single-blind (rated as low quality). Blinding was not clear for the remaining 11 trials. 54 of the included trials were rated as high quality in terms of random sequence generation; the corresponding numbers were 24 for allocation concealment; 70 for blinding of outcome assessment; 95 for incomplete outcome data; and 127 for selective reporting. A large number of trials were considered to have uncertain methodological quality: 94 trials for random sequence generation; 77 for allocation concealment; 46 for blinding of outcome assessment; 48 for incomplete outcome data; and 11 for selective reporting.

On average, the included set of randomized controlled trials had between two and three methodological attributes with high quality (average methodological quality score across the included set of trials was 2.65). There were 14 trials that did not have any methodological attributes with high quality; 38 trials had one; 37 had two, 38 had three; 30 had four; and 14 had five. Only 11 trials were rated as having high quality on all six methodological quality attributes.

### 7.5.1 *Distribution of Methodological Quality in the Evidence Network*

Figure 7.3 shows the distribution of methodological quality scores among the eligible comparisons of statins and control treatment. The majority of comparisons had an average methodological score between two and three (depicted in black lines in Figure 7.3). On average, placebo-controlled trials of rosuvastatin and simvastatin had higher methodological quality than other comparisons (average methodological quality score for both comparisons >3). Trials comparing atorvastatin and fluvastatin (two trials, average methodological quality score: 1.50); atorvastatin and rosuvastatin (34 trials, score: 1.97); atorvastatin and simvastatin (24 trials, score: 1.79); fluvastatin and pravastatin (one trial, score: 1.00); fluvastatin and simvastatin (two trials, score: 1.30); lovastatin and simvastatin (three trials, score: 1.66); and pravastatin and simvastatin (10 trials, score: 1.80) were rated as having very low methodological quality.

**Figure 7.3** – Distribution of methodological quality in the network of available statin and control comparisons.\*

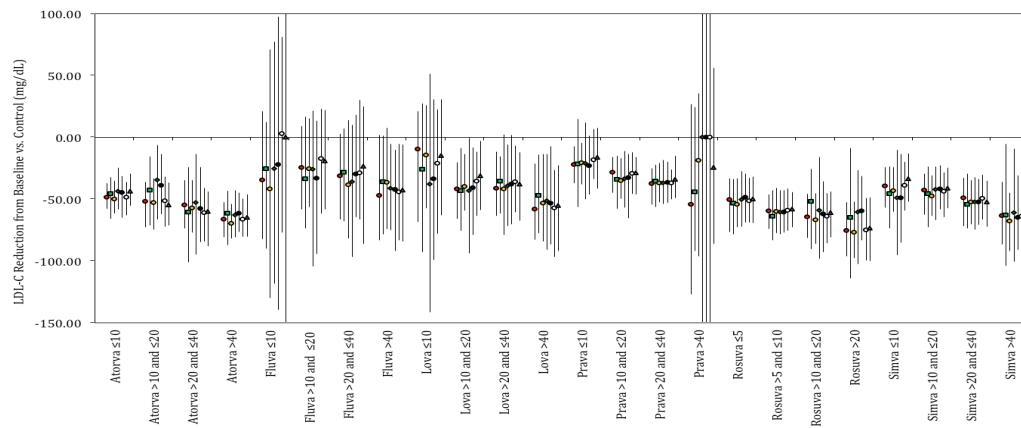


\* Connecting lines indicate the direct pair-wise comparisons between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants receiving the named statin. Color of the line connecting the nodes is indicative of the average methodological quality of the trials directly comparing the two treatments: red denotes very low quality (average methodological quality score of trials <2); black, low quality (average methodological quality score of trials: ≥2 and <3); and green, moderate quality (average methodological quality score of trials ≥3).

#### 7.5.2 Influence of Methodological Quality Attributes on Dose-Comparative Effects

Figure 7.4 shows the sensitivity of the dose-comparative effects of individual statins to different trial-level methodological quality attributes. Overall, the magnitude of cholesterol-lowering effects of statin therapy vs. control was consistent when trials with low quality were excluded in various sensitivity analyses. The degree to which the magnitude of cholesterol reduction varied across analyses depended greatly on the amount of the data available for a given analysis. In cases where there were few data points available (for example, fluvastatin at all dose formulations; lovastatin at ≤10 mg/day; and pravastatin at >40 mg/day), there was considerable uncertainty around the observed treatment effects. In all analyses, 95% CrIs greatly overlapped across base-case and sensitivity analyses.

**Figure 7.4** – Sensitivity of network meta-analysis findings to methodological quality attributes of randomized controlled trials of statins.\*



\* Figure shows mean change from baseline LDL cholesterol levels with individual statins at different doses as compared to control (95% credible intervals); lower (more negative) values favor statin treatment over control. In addition to the findings of the base-case analysis shown in red (circles), findings of separate sensitivity analyses excluding trials with low quality on the following methodological quality attributes are shown: blinding (green squares); random sequence generation (yellow circles); allocation concealment (blue diamonds); blinding of outcome assessment (black circles); incomplete outcome data (white circles); and selective reporting (purple triangles).

## 7.6 Risk of Industry Sponsorship Bias in the Randomized Controlled Trials of Statins

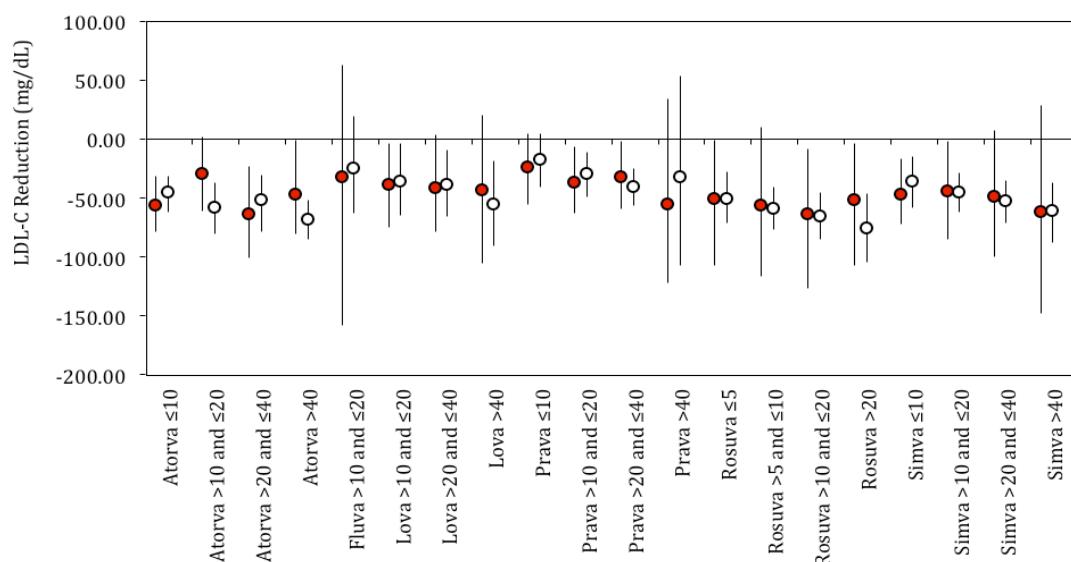
A total of 136 randomized trials were sponsored by the pharmaceutical industry. 17 trials were sponsored by governmental agencies, and eight were funded by academic research centers. The remaining 15 trials did not report the funding source. Out of a total of 136 industry-sponsored trials, 58 were placebo-controlled (42.6%). The corresponding number for the nonindustry-sponsored trials was 17 (42.5%). There were 31 multi-armed industry-sponsored trials as compared to eight multi-armed nonindustry-sponsored trials. Out of a total of 66 statin and dose comparisons available in 40 nonindustry-sponsored trials (including multiple comparisons in multi-armed trials), 39 were unique comparisons. 33 of the unique comparisons were also available in industry-sponsored trials (Table 7.2).

There were no systematic differences between the findings obtained from industry-sponsored and nonindustry-sponsored trials (Figure 7.5). While the network meta-analysis of industry-sponsored trials estimated a larger treatment effect for some statin-dose combinations as compared to the network meta-analysis of nonindustry-sponsored trials (for example, the mean reduction from baseline with atorvastatin >20 and ≤40 mg/day vs. control was an estimated 63.34 mg/dL as compared to an estimated 50.96 mg/dL in nonindustry-sponsored trials), the opposite was true in other cases (for example, the mean reduction from baseline with atorvastatin ≤10 mg/day vs. control was an estimated 45.19 mg/dL in industry-sponsored trials as compared to an estimated 55.74 mg/dL in nonindustry-sponsored trials). There was generally greater uncertainty around the cholesterol-lowering effects of individual statins in nonindustry-sponsored trials, reflecting the smaller number of randomized controlled trials that were funded by nonindustry sources. Overall, point estimates and 95% credible intervals greatly overlapped for all statin-dose combinations included in both sets of network meta-analyses.

**Table 7.2** – Availability of statin-dose comparisons in industry and nonindustry-funded trials.

Unique comparisons available in nonindustry-sponsored trials	Availability in industry-sponsored trials
Atorvastatin 10 mg/day vs. placebo	Yes
Atorvastatin 10 mg/day vs. atorvastatin 80 mg/day	Yes
Atorvastatin 10 mg/day vs. lovastatin 20 mg/day	Yes
Atorvastatin 10 mg/day vs. pravastatin 20 mg/day	Yes
Atorvastatin 10 mg/day vs. rosuvastatin 5 mg/day	Yes
Atorvastatin 10 mg/day vs. simvastatin 10 mg/day	Yes
Atorvastatin 10 mg/day vs. simvastatin 20 mg/day	Yes
Atorvastatin 20 mg/day vs. placebo	No
Atorvastatin 20 mg/day vs. atorvastatin 80 mg/day	Yes
Atorvastatin 20 mg/day vs. rosuvastatin 10 mg/day	Yes
Atorvastatin 40 mg/day vs. simvastatin 40 mg/day	Yes
Atorvastatin 40 mg/day vs. rosuvastatin 20 mg/day	Yes
Atorvastatin 80 mg/day vs. pravastatin 40 mg/day	Yes
Fluvastatin 10 mg/day vs. placebo	No
Fluvastatin 10 mg/day vs. fluvastatin 20 mg/day	No
Fluvastatin 20 mg/day vs. placebo	Yes
Lovastatin 20 mg/day vs. placebo	Yes
Lovastatin 20 mg/day vs. lovastatin 40 mg/day	Yes
Lovastatin 20 mg/day vs. pravastatin 20 mg/day	No
Lovastatin 20 mg/day vs. simvastatin 10 mg/day	Yes
Lovastatin 40 mg/day vs. placebo	No
Pravastatin 10 mg/day vs. placebo	Yes
Pravastatin 10 mg/day vs. pravastatin 20 mg/day	Yes
Pravastatin 10 mg/day vs. pravastatin 40 mg/day	Yes
Pravastatin 10 mg/day vs. simvastatin 10 mg/day	Yes
Pravastatin 20 mg/day vs. placebo	Yes
Pravastatin 20 mg/day vs. pravastatin 40 mg/day	Yes
Pravastatin 40 mg/day vs. placebo	Yes
Pravastatin 40 mg/day vs. pravastatin 80 mg/day	No
Pravastatin 80 mg/day vs. placebo	Yes
Rosuvastatin 10 mg/day vs. placebo	Yes
Rosuvastatin 10 mg/day vs. simvastatin 20 mg/day	Yes
Rosuvastatin 10 mg/day vs. rosuvastatin 20 mg/day	Yes
Rosuvastatin 20 mg/day vs. placebo	Yes
Simvastatin 10 mg/day vs. placebo	Yes
Simvastatin 10 mg/day vs. simvastatin 20 mg/day	Yes
Simvastatin 20 mg/day vs. placebo	Yes
Simvastatin 20 mg/day vs. simvastatin 40 mg/day	Yes
Simvastatin 40 mg/day vs. placebo	Yes

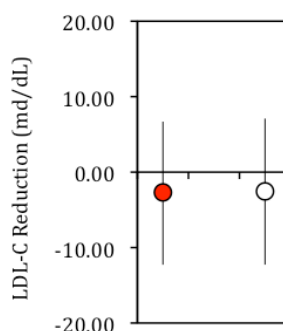
**Figure 7.5 – Dose comparative effects of statins on serum LDL cholesterol levels in industry- vs. nonindustry-sponsored trials.\***



\* Findings from industry-sponsored trials are shown in white and findings from nonindustry-sponsored trials are shown in red. Estimates shown are mean changes from baseline (95% credible intervals) in serum LDL cholesterol concentrations as compared to control treatment.

Figure 7.6 shows the magnitude of mean industry sponsorship bias, as obtained from the meta-regression analysis. There was no clear evidence of industry-sponsorship bias: the mean change from baseline LDL cholesterol levels was exaggerated on average by 2.69 mg/dL (95% CrI: -12.27, 6.69) in scenario 1 and 2.55 mg/dL (95% CrI: -12.26, 7.10) in scenario 2.

**Figure 7.6** – Meta-regression analysis results: Evaluation of industry sponsorship bias in the randomized controlled trials of statins.\*



\* Findings of scenario 1 are shown in red and findings of scenario 2 are shown in white. Figure shows the extent to which mean change from baseline LDL cholesterol levels was exaggerated in trials with industry-favored statins (95% credible intervals); lower (more negative) values suggest greater bias.

## 7.7 Summary and Discussion

The Cochrane Collaboration defines bias as a systematic deviation from the truth, in results or inferences of studies.<sup>455</sup> In other words, bias refers to *systematic error*, suggesting that multiple replications of the same trial would reach the wrong answer on average. Although randomized research designs are largely immune to many biases that affect weaker forms of evidence obtained from nonrandomized studies, important deficits in the design, conduct, analysis, and reporting may still lead to bias in randomized controlled trials.<sup>415</sup> The empirical work presented this chapter explored the methodological quality and risk of industry sponsorship bias in the randomized controlled trials of statins.

Consistent with the literature evaluating the risk of bias due to reported design characteristics of randomized trials,<sup>429,430</sup> the analyses presented in this chapter did not detect any effect of methodological flaws on an objective laboratory outcome. Specifically, the magnitude of LDL cholesterol-lowering effects of individual statins was consistent when trials with low methodological quality attributes were excluded from various sensitivity analyses.

There is now a long history of studies evaluating industry sponsorship bias, which unequivocally conclude that industry sponsorship biases study outcomes in favor of the sponsoring company's product.<sup>435-438,440,456</sup> As Bero put it, "Decision makers should take sponsorship into account when evaluating whether they should base clinical practice and reimbursement on the results of a trial."<sup>438</sup> Sismondo added: "Funding introduces a systematic bias that cannot be corrected by simple methodological strictures."<sup>434</sup> He went

even further and concluded that there was no more need for research to establish that funding affects published results.

Previous reviews outlined a number of potential mechanisms by which industry sponsors can influence the outcome of a study, including how the trial is designed, conducted, analyzed, and reported. Given the conclusive evidence that the methodological quality of industry-sponsored trials is at least as good as (and often times better than) those sponsored by nonindustry sources,<sup>437</sup> the observed “industry sponsorship bias” may be attributable of factors that cannot be explained by standard risk of bias assessment tools.

Unlike the findings of the previous reviews, the analyses presented in this chapter did not find empirical evidence of industry sponsorship bias in a systematically identified set of placebo-controlled and active-comparator trials of statins. First, the mean change from baseline LDL cholesterol levels achieved in industry-sponsored trials closely paralleled in magnitude the reductions observed in nonindustry-sponsored trials: there was no evidence that pharmaceutical sponsors favored their own drugs in placebo-controlled or active-comparator trials of statins. As shown in Chapter 4 (*Dose-Comparative Effects of Statins on Cholesterol Levels*), there were actual differences in the effectiveness of individual statins at different doses that, when taken into account, explained previously observed differences between industry- and nonindustry-sponsored trials. Second, there was limited evidence that pharmaceutical companies addressed research questions that were drastically different than those asked by other funders. For example, a similar share of industry- and nonindustry-sponsored statin trials was placebo-controlled. In addition, out of a total of 39 unique statin-dose comparisons available in nonindustry-sponsored trials, 33 were also available in industry-sponsored trials, potentially reflecting the relevance of research conducted by industry sponsors.

The assessment of industry sponsorship bias presented in this chapter differed from previous reviews in the literature in the following ways:

1. *Comparison of like with like.* Previous studies did not limit their comparisons to a homogenous set of studies. The analyses presented in this chapter paid particular attention to the comparability of patient populations, interventions, and doses across the identified set of trials.<sup>447</sup> As discussed in Chapter 3 (*Evidence Review and Synthesis Methods*), a systematic review was performed to identify randomized controlled trials of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin if they had more than 50 participants per trial arm, lasted longer than four weeks, and reported the outcomes of interest as defined in a protocol that was developed prior to the review. Included trials were those in patient populations with and without coronary heart disease at baseline. Unlike previous analyses, which explored the potential effect of industry sponsorship on a heterogeneous

range of objective and subjective outcomes, the current review adopted mean LDL cholesterol reduction from baseline as the primary outcome of interest to ensure consistency across the included set of trials. Also, mean LDL cholesterol reduction from baseline was the most frequently reported outcome in the randomized controlled trials of statins. Another important advantage of using this outcome was its objective nature. As previous meta-epidemiological studies have shown,<sup>429,430</sup> objective outcomes such as laboratory assessments are largely immune to biases resulting from methodological quality deficits in trials.

*2. Exploration of the mechanism of potential bias.* Previous studies did not explore the potential mechanism of potential bias. Gartlehner and colleagues were among the first to point out the difficulty in determining how industry biases from multiple funding sources would influence a complex body of evidence, with different companies sponsoring different products.<sup>448</sup> In a best-case scenario, they postulated that biases from multiple funding sources would act in opposing directions and cancel each other out. In a worst-case scenario, Gartlehner and colleagues paralleled the notions put forth by Barden and colleagues in that if industry bias exists, a drug would perform better in trials sponsored by its manufacturer and worse as a comparator in trials funded by a competitor.<sup>447</sup> Applying these considerations to the statin evidence network, analyses presented in this chapter evaluated the particular mechanism of potential industry sponsorship bias. Specifically, the hypothesis tested in this chapter was that industry sponsorship bias would occur when a pharmaceutical sponsor favored its own product in placebo-controlled or active-comparator trials, or the highest dose of its own drug in a trial comparing multiple doses. Based on these analyses, there was no evidence that the pharmaceutical companies intentionally favored their products in the randomized controlled trials of statins.

*3. Comparison of effect sizes.* Previous influential reviews did not evaluate the magnitude of effect sizes. They showed that there was a statistical association between industry sponsorship and positive results.<sup>435-437</sup> Positive results observed in earlier studies referred to a dichotomous outcome of either reporting statistically significant findings or positive conclusions that were favorable for the sponsoring company. These approaches may be subject to important limitations. For the former, industry sponsorship may result in larger and better-designed studies (as shown in the trials in psychiatry),<sup>457</sup> with greater statistical power to identify significant differences if such differences exist. For the latter, Als-Nielsen and colleagues showed that source of funding is a good predictor of the strength of published recommendations (also referred to as ‘interpretation bias’).<sup>456</sup> (As discussed under item 4 below, the question of whether favorable conclusions are inappropriate cannot be addressed without taking into account actual treatment differences between statins.) Strictly speaking, the difference in the frequency of either statistically significant findings or

favorable conclusions observed between industry- and nonindustry-sponsored trials should not be referred to as bias. Bias is the underestimation or overestimation of true intervention effects. Therefore, any bias assessment would need to evaluate the *magnitude* of the intervention effect (as well as its uncertainty).

Indeed, when the magnitude of the intervention effect was taken into account, the empirical work presented in this chapter showed that industry-sponsored trials of statins resulted in the same degree of cholesterol reduction, as did nonindustry-funded trials.

4. *Consideration of actual effectiveness differences between treatments and doses.* Previous reviews did not test differences in effectiveness that can be explained by different drugs and their dosages. Heres and colleagues showed that previous comparisons of the same set of antipsychotic drugs led to contradictory overall conclusions, depending on the sponsor of the study.<sup>450</sup> Safer and colleagues reported that in trials of psychiatric drugs the comparator drug was often given in doses outside the usual range or there was a rapid and substantial dose increase in the drug not manufactured by the sponsoring company, indicating deliberate scientific misconduct.<sup>458</sup> As Lexchin noted, higher doses may bias the results in favor of effectiveness of the manufacturer's product.<sup>436</sup> These previous analyses suggested that treatment and dose differences should be taken into account in analyses exploring bias. Network meta-analysis provides a methodological framework for dose and different statins being used.<sup>451,452</sup> The analyses presented in this chapter allowed for the incorporation of actual differences in the effectiveness of individual statins at different doses. When such differences were taken into account, there was no evidence of industry sponsorship bias within individual trials.

#### 7.7.1 *Generalizability of Findings*

An important consideration is whether the findings of this chapter are generalizable to the assessment of industry sponsorship bias in other therapeutic areas. Certainly, there are unique aspects of the statin evidence base that complicate comparisons with other therapeutic areas. Lathyris and colleagues previously suggested that the more favorable results of industry-sponsored trials might be due to design issues, in particular the choice of comparators that are either inactive or suboptimal.<sup>449</sup> Unlike other therapeutic areas where the influence of dose on treatment effectiveness may not be widely known outside of industry researchers, statin drugs have a widely established dose-response relationship with higher doses resulting in greater cholesterol lowering effects. It is possible that this relationship might have made it difficult for pharmaceutical companies to introduce overt design biases in randomized controlled trials using dose as a design factor. This may explain why the comparators in industry- and nonindustry-sponsored trials greatly overlapped in the statin evidence network. Out of a total of 39 unique comparisons available in

nonindustry-sponsored trials, 33 were also available in industry-sponsored trials. Interestingly, fluvastatin at  $\leq 10\text{mg/day}$ , one of the least effective statins, was avoided in industry-sponsored trials.

Previous studies have shown that each pharmaceutical company generates a clinical research agenda that is strongly focused on its own products, while comparisons involving different interventions from different companies are uncommon. Indeed, Lathyris and colleagues showed that the large majority of industry-sponsored randomized research is sponsored by a single company and examines a single intervention owned by this company.<sup>449</sup> In addition, according to the review by Lathyris and colleagues head-to-head comparisons of interventions owned by different companies are a small minority of industry-sponsored trials. However, this was not the case in the clinical literature evaluating the effectiveness of statin therapy, which may limit the generalizability of the findings presented in this chapter to other therapeutic areas. There were a large number of trials where pharmaceutical companies compared their products against licensed regimens belonging to other companies. However, consistent with the findings of the review by Lathyris and colleagues,<sup>449</sup> in head-to-head trials of statins, the company owning the established comparator was usually not involved.

More problematic is the pharmaceutical company behavior in terms of publication delays and data withholding, contributing to time-lag and publication biases.<sup>459,460</sup> In recent years, pharmaceutical companies have attempted to prevent studies with unfavorable results from being published, and to publish positive results more than once in high profile cases.<sup>441,461</sup> Such practices, which do not appear to be prevalent in the statin literature,<sup>462</sup> may partly explain the previous findings of bias in favor of outcomes of research funded by industry.<sup>461</sup>

### *7.7.2 Bias in an Individual Trial vs. a Collection of Trials*

The findings of this chapter suggested that the research questions asked by industry sponsors seem to parallel those asked by nonindustry sources, and the findings obtained from these trials appear similar in magnitude as those in nonindustry sources. Nonetheless, as shown in previous reviews, pharmaceutical companies exclusively sponsor trials that have favorable conclusions for its products. This has clear implications for those reviewing and making decisions based on the existing evidence. Industry sponsorship creates asymmetries in the evidence base, with some companies selectively comparing their products against others that they deem strategic competitors. For example, all of the direct head-to-head comparisons between rosuvastatin, which entered the United States market in 2003 (sponsoring company: Astra Zeneca), and atorvastatin, which was approved by the Food and Drug Administration in 1996 (sponsoring company: Pfizer), were funded by Astra Zeneca. In a similar fashion, Pfizer sponsored the majority of head-to-head trials of

atorvastatin and earlier statins. Over the quarter century history of statins, the manufacturer of every newcomer statin principally targeted the next best option (which was likely identified based on market share at the time) and pursued it as a comparator in almost all of its head-to-head randomized controlled trials, reflecting the research and development strategies of pharmaceutical companies.

Even so, such a research and development strategy appears to have had both advantages and disadvantages in the case of the statin evidence network. Overall, every trial provided a piece of a puzzle that, when taken together, provided a relatively symmetric and balanced evidence network for statins (albeit the small number of trials available for some statins such as fluvastatin and lovastatin). Unlike other therapeutic fields,<sup>463,464</sup> the randomized controlled trial evidence base of statins included a large number of head-to-head trials providing information on a range of doses. Nonetheless, there is a risk to derive biased conclusions about the comparative effects of individual statins. For instance, a meta-analysis failing to take into account dose differences between individual statins would produce biased results. A more appropriate approach would be to synthesize the entirety of the evidence network that includes all placebo-controlled and active-comparator trials of statins that provide direct and indirect information for all treatment contrasts of interest at different doses – as has been done in this thesis.

## Chapter 8

### Evidence-Based Decision-Making: Going from Evidence to Prescribing\*

As outlined in Chapter 1 (*Introduction: The Concept of Quality in Prescription Drug Therapy*), defining prescribing quality on the basis of comparative evidence requires prescribers to appraise all available evidence prior to reaching a conclusion about which drug to prescribe. In principle, quantitative comparative effectiveness data have the potential to provide prescribers with valuable evidence to make an effective choice out of several apparently similar drugs. The empirical work presented in this thesis focused on the role of evidence review and synthesis methods to generate comparative evidence on individual statins, which can subsequently be used to guide and evaluate the quality of statin prescribing decisions. This chapter reflects on the potential utility of comparative evidence to decision-making, and outlines a number of considerations to apply such evidence in prescription drug therapy, i.e., to fill the existing gaps in clinical practice guidelines; and facilitate evidence-based decision-making. Specifically, this chapter brings together the empirical findings of the previous chapters and addresses the following questions:

1. What are the limitations and strengths of the methods underpinning the empirical findings?
2. Should prescribers recommend statin therapy?
3. Which statin(s) should be favored in clinical practice?
4. What are some generalizability considerations when applying the findings of this systematic review and network meta-analysis to individuals in clinical practice?

The first part of this chapter summarizes the methods underpinning the empirical findings of this thesis, and lists their limitations and strengths. The second part provides a discussion on the primary clinical practice implications of the findings, and explores the potential role

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\* Part of the contents of this chapter is currently under review with the following reference: Naci H, Valkenhoef G, Higgins JPT, Fleurence R, Ades AE. Evidence-based prescribing: Using existing data on clinical benefits and harms to choose among drugs. Under Review.

of multi-criteria decision analysis in improving the interpretability of network meta-analysis findings. The final part outlines important generalizability considerations.

### **8.1 Summary of Empirical Considerations**

The systematic review of the clinical literature on statins, which forms the empirical basis of this thesis, included randomized controlled trials of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin if they had more than 50 participants per trial arm, lasted longer than four weeks, and reported the outcomes of interest as defined in the study protocol. Of particular interest were the effects of individual statins in the primary and secondary prevention of all-cause mortality, major coronary events, and major cerebrovascular events, and discontinuations due to adverse events, myalgia, transaminase elevations, and creatine kinase elevations. As described in Chapter 3 (*Evidence Review and Synthesis Methods*) the statistical analyses predominantly consisted of Bayesian network meta-analysis methods to synthesize the available direct and indirect evidence on individual statins.<sup>284</sup>

Overall, the systematic review of the published literature included 184 randomized controlled trials with 260,630 individuals with or without cardiovascular disease at baseline. Although a large number of existing trials were placebo-controlled ( $n = 85$ ), 99 head-to-head trials compared statins at different doses and investigated the comparative benefits and harms of individual statins. There was an apparent asymmetry in the evidence network where specific interventions were more commonly evaluated (e.g. atorvastatin) than others (e.g. fluvastatin). Most frequent comparisons occurred between pravastatin and placebo, atorvastatin and placebo, and rosuvastatin and atorvastatin. No trial directly compared all six statins to each other.

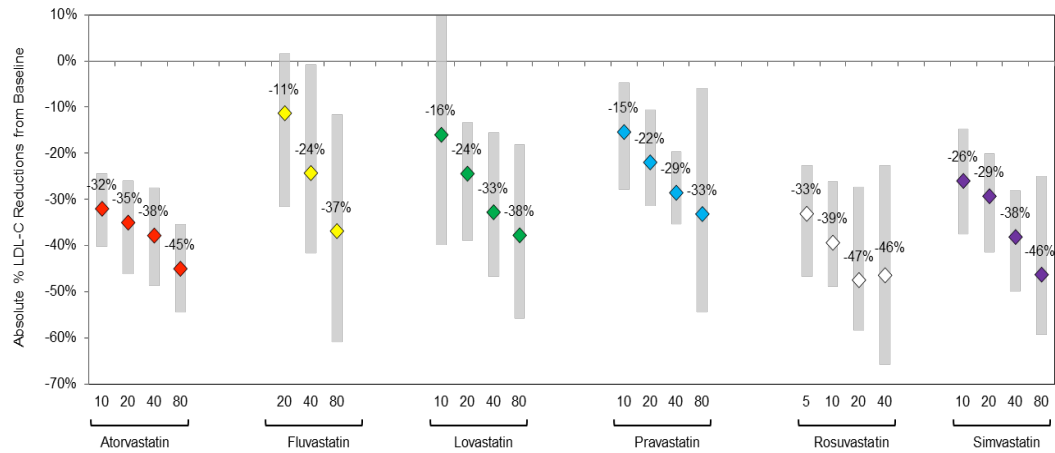
The network meta-analysis approach used to determine the comparative benefits and harms of individual statins assumed similarity and consistency in the evidence base. Underpinning both of these considerations was the assumption that there was no interaction between heterogeneity and treatment comparisons. This implies that heterogeneity that is unexplained or unaccounted for may introduce bias if it influences different statins to a different extent.<sup>288</sup> As described by Jansen and Naci, any imbalances across studies in terms of unmeasured or unknown relative effect modifiers would bias the results.<sup>308</sup> Hence, any comparison of individual statins should be tempered by the differences that may result from imbalances in the distribution of relative treatment effect modifiers across different trials.

In order to ensure similarity and consistency across the entire set of trials included in the systematic review, both statistical and qualitative approaches were adopted. First, all analyses were based on random-effects models, which took into account potential

heterogeneity and resulted in wide 95% credible intervals (i.e. yielded more conservative estimates as compared to estimates obtained from a fixed-effect model). Second, for potential relative treatment effect modifiers that were dichotomous variables, such as coronary heart disease status, subgroup analyses were conducted. Third, meta-regression analyses were performed to explain heterogeneity in terms of differences in study-level covariates (e.g. baseline mean age, baseline mean LDL cholesterol concentration, trial publication year). The meta-regression analyses suggested that the comparative benefits and harms of individual statins were not sensitive to differences in study-level relative treatment effect modifiers. Specifically, these analyses did not detect a statistically significant impact of publication year and mean age of patients at baseline on the comparative benefits and harms of statins. The findings were consistent with previous reviews showing that the clinical benefits of statins might vary modestly across differing levels of baseline LDL cholesterol levels. To formally evaluate consistency in the treatment network, the magnitude and direction of effect sizes obtained from direct and indirect comparisons were both qualitatively and quantitatively compared, confirming that there was no detectable inconsistency in the existing evidence base for statins.

The effect of dose on comparative treatment effects of statins was an essential consideration in network meta-analyses. In particular, the analyses considered the impact of dose in a number of different ways: in addition to excluding trials with high-dose formulations to obtain doses with comparable LDL cholesterol lowering effects for different statins (for analyses of clinical benefit outcomes), separate analyses were performed to compare individual statins at low, medium, and high doses. Similarity or interchangeability of statin doses was examined by a statistical analysis of LDL cholesterol lowering effects at different doses, as shown in Figure 8.1 below (also reported in Chapter 4: *Dose-Comparative Effects of Individual Statins on Cholesterol Concentrations*).

**Figure 8.1** – Dose-comparative absolute effects of statins on serum LDL cholesterol concentrations.\*



\* Estimates shown are absolute reductions at all dose combinations standardized to the average pretreatment LDL cholesterol concentration in the included set of trials (mean, 95% CrIs).

## 8.2 Limitations and Strengths of Methods

Network meta-analyses reported in this thesis were not without limitations. First, as a literature-based meta-analysis, the empirical findings shared the limitations of the published evidence base. Using the Cochrane Collaboration’s tool for assessing the risk of bias in randomized trials,<sup>415</sup> only a few trials were rated as high quality on all methodological quality attributes. Overall, the quality of reporting for the included randomized trials was well below an acceptable level, which complicated the assessment of their methodological conduct and validity.<sup>465</sup> Accordingly, as reported in Chapter 7 (*Methodological Quality and Risk of Industry Sponsorship Bias in the Randomized Controlled Trials of Statins*), a large number of trials were rated as “uncertain quality”: it was challenging to distinguish between methodological factors that were missing (such as lack of allocation concealment) and those that were simply not reported – a commonly encountered problem in systematic reviews of the literature.<sup>88-90</sup> Given that standardized reporting checklists for randomized trials are relatively new (e.g. Consolidated Standards of Reporting Trials, [CONSORT]<sup>466</sup>), older randomized controlled trials may not have reported important design features, even when they were carried out. In this regard, it may not be fair to apply the same quality criteria to older clinical trials that were conducted in a period during which reporting standards were different (or not as detailed). The systematic review conducted for this thesis was particularly prone to this limitation given the long history of statin trials, spanning over 25 years.

Irrespective of methodological quality assessments, however, the fundamental consideration in a network meta-analysis is whether an estimate of treatment effect is near the “true” value for a given outcome, across studies. It is significant to consider the extent to which results of included trials (and their synthesis across a complex evidence network) are trustworthy and should be believed. The analysis presented in Chapter 7 (*Methodological Quality and Risk of Bias in Randomized Controlled Trials of Statins*) showed that the findings of the randomized trials of statins did not appear to be influenced by reported deficits in trial methodology. Also, there was no qualitative or statistical evidence to suggest that industry-sponsorship resulted in a systematic underestimation or overestimation of the true intervention effect across the evidence network.

Second, while there were several active-comparator trials comparing statins in terms of LDL cholesterol lowering effects or harm outcomes, there were only a few direct head-to-head trials of statins that were prospectively designed to capture differences in clinical benefit outcomes as primary endpoints. Related to this point, there was an apparent asymmetry in the evidence network where specific interventions appeared to be avoided. In particular, there was a paucity of existing data on benefits and harms for fluvastatin. For instance, the relative effect of fluvastatin on creatine kinase elevations was estimated on the basis of only eight events observed in four trials including 2,646 participants. Similarly, there were only four trials of fluvastatin, which reported hepatic transaminase elevations, introducing considerable uncertainty (as evident in extremely wide 95% credible intervals) into the comparative treatment effects of this agent. When present, such uncertainty weakened the conclusions that could be drawn on the comparative benefits and harms of individual statins.

Third, there was inadequate data for a meaningful comparison of individual statins in primary and secondary prevention. For instance, there was no available all-cause mortality data on simvastatin among individuals without established coronary heart disease; no data on the effect of fluvastatin and simvastatin on major coronary events in primary prevention; and no data on the effect of fluvastatin and rosuvastatin on major coronary events in secondary prevention. Also, the total number of trial participants eligible for inclusion in sub-group analyses by coronary heart disease status was considerably less than the total number of eligible participants included in base-case analyses including all populations (overall population). As a result, there was considerable uncertainty in the relative treatment effects in sub-groups with correspondingly wide 95% credible intervals and unstable ranking probabilities – again potentially weakening the clinical interpretability of network meta-analysis findings.

Finally, as with any meta-analysis, it remains a possibility that the analysis did not fully account for heterogeneity due to unobserved or unmeasured factors. Given the large volume of available studies in the literature, the network meta-analyses did not use individual patient-level data, which would have advantages when exploring potential differences across relative treatment effect modifiers.<sup>470</sup> Having access to individual patient-level data would offer additional benefits, as discussed in Chapter 9: *Future Research Directions, Policy Implications, and Conclusions*.

In spite of these limitations, the empirical work presented in this thesis had important strengths. This systematic review of the literature was the largest and most comprehensive meta-analysis on statin therapy, and the first to investigate the comparative effects of different statins using both placebo-controlled and active-comparator trials. Using network meta-analysis methods were particularly helpful in two important ways. First, these methods facilitated the incorporation of the totality of the existing data obtained from identified randomized controlled trials, allowing for an in-depth investigation of the comparative benefits and harms of individual statins. Second, network meta-analyses allowed for ranking individual statins on the basis of both benefit and harm outcomes.

This analyses presented in this thesis differed from previous network meta-analyses in three important aspects. First, it incorporated data from a comprehensive list of trials irrespective of placebo or active controls. Although a large number of randomized controlled trials compared statins head-to-head, until the empirical work presented in this thesis, findings of these active-comparator trials were neither systematically identified nor combined with the findings of placebo-controlled trials. Previous meta-analyses were pair-wise in nature, which, by definition, compared two alternatives at a time. Even previous attempts at analyzing the comparative benefits and harms of multiple statins did not identify and include active-comparator trials.<sup>105,214,348,359,392</sup> Over the quarter-century history of statins, there had not been any comprehensive review of the existing literature evaluating whether individual statins (irrespective of their cholesterol-lowering effects) are different in terms of their benefit and harm profiles.

Second, although limited by data availability, this review attempted to provide comparative estimates separately for the primary and secondary prevention populations. This was a key strength of the analyses presented in this thesis because statin therapy, initially focused on patients with established coronary heart disease, has become widely common as the limits of treatment expanded over time to include persons at progressively lower risk of developing cardiovascular events. As the number of people eligible for statin therapy continues to increase, information regarding the relative clinical value of statins is needed to better inform patients and prescribers. It is particularly difficult to determine the exact

threshold of the level of baseline risk for cardiovascular events at which to start prescription or tailor therapy to patients most likely to benefit from statin treatment. Findings presented in this thesis provide additional evidence to support decision-making in clinical practice.

Third, the comparative efficacy and side effects of individual statins were evaluated at different doses. The majority of previous meta-analyses did not explicitly address the potential impact of dose on the clinical efficacy and safety of statins. The empirical findings presented in this thesis provide essential information to prescribers about the comparative benefits and harms of individual statins.

### **8.3 Benefits and Harms of Statins as a Class: Whether to Prescribe Statins?**

The empirical analyses presented in this thesis provide relevant evidence not only to investigate the comparative benefits and harms of individual statins but also to answer important questions not fully addressed in previous reviews. One such question is whether statins should be prescribed for individuals without established coronary disease (primary prevention population). Although the therapeutic value of statins in the secondary prevention setting are well documented, their effectiveness in individuals free of coronary heart disease is disputed.<sup>237</sup> The empirical work presented in Chapter 5 (*Comparative Benefits of Individual Statins*) showed that all-cause mortality benefits of statins were clinically and statistically significant in this population. With reductions estimated at 9%, this analysis confirmed the survival benefit of statin therapy observed in some of the previous meta-analyses.<sup>257</sup> In contrast to recent reviews,<sup>221</sup> this analysis achieved a higher precision around the survival benefit (with statistical significance) as a result of including trials with very few events that were not considered previously. This finding also closely paralleled the most recent individual patient-level meta-analysis performed by the Cholesterol Treatment Trialists that showed that using statins was effective in the primary prevention setting,<sup>238</sup> providing empirical evidence in support of the emerging consensus among experts<sup>471</sup> that statins should be prescribed to individuals who have a moderate-to-high 10-year risk of developing coronary heart disease, as estimated by risk assessment tools commonly used by prescribers in clinical practice.<sup>472</sup>

While the findings reported in Chapter 5 (*Clinical Benefits of Individual Statins*) provided supporting evidence for initiating statin therapy in individuals who are at an increased risk of developing cardiovascular disease, findings reported in Chapter 6 (*Comparative Harms of Individual Statins*) suggested that expanding the limits of statin therapy to a wider population of individuals without cardiovascular disease might have important safety implications. Although rare, adverse events associated with statin therapy range from mild to moderate, and appear to increase with treatment intensity. With notable exceptions,<sup>473</sup>

randomized trial evidence on the long-term safety of individual statin treatments remains limited. At the population level, mortality and cardiovascular benefits of statin therapy in primary prevention greatly outweigh its potential harms – even taking into account the recent finding that statin use is associated with a modest increase in diabetes incidence (Approximately 260 individuals would need to be treated with statins for about four years for one case of diabetes to develop. In contrast, an estimated 50 individuals would need to be treated for about four years to prevent one major coronary event).<sup>371</sup> At the individual level, however, there may be a risk of exposing a large group of individuals to the (primarily minor) harms of statin therapy for the benefit of a smaller number of individuals. In addition to new-onset diabetes, statins use is linked to (asymptomatic and reversible) liver enzyme elevations. At high doses, statins are not very tolerable with patients discontinuing treatment due to adverse events such as reversible enzyme elevations potentially indicative of muscle injury or damage. Although the risk of developing diabetes is low, what this risk would amount to over time is simply not known based on the existing evidence base. Taken together, the empirical findings reported in this thesis suggest that statins should not be enthusiastically recommended for individuals at low risk of developing coronary heart disease.<sup>161</sup> In addition, compelling evidence suggests that non-pharmacological interventions may be as effective as drug therapy in many chronic illnesses, including coronary heart disease.<sup>474</sup> Such interventions may substitute or complement drug therapy in individuals at low risk of developing coronary heart disease.

#### **8.4 Comparative Benefits and Harms of Individual Statins: Which Statin to Prescribe?**

“What is the drug of choice for condition x?” is among the most commonly asked questions in primary care.<sup>475</sup> Reflecting the complexity of prescribing decisions, answering this question requires a difficult trade-off between the benefits and harms of multiple drugs for a given condition. In the case of statin therapy for the primary and secondary prevention of coronary heart disease, there are several important benefit and harm outcomes, which include all-cause mortality, major coronary events, major cerebrovascular events (in terms of benefit outcomes), and discontinuations due to adverse events, myalgia, hepatic transaminase elevations, creatine kinase elevations, and most recently, new-onset diabetes (in terms of harm outcomes).

One conceivable way to simplify therapeutic considerations for choosing among different statin options would be to prioritize major coronary events and discontinuations due to adverse events over other benefit and harm outcomes. Such an approach (albeit hypothetical) would be justifiable on the grounds that prevention of major coronary events is among the fundamental goals of statin therapy: although not always fatal, major coronary events often result in severe pain and lifelong disability. In a similar fashion, monitoring and

minimizing discontinuations due to adverse events is an important aspect of prescription drug therapy since this outcome is indicative of the acceptability and tolerability of pharmacological treatment and encompasses a range of reasons for withdrawing treatment because of side effects.

According to the findings presented in Chapters 5 (*Comparative Benefits of Individual Statins*) and 6 (*Comparative Harms of Individual Statins*), there were a number of statistically detectable differences among individual statins in terms of both major coronary events and discontinuations due to adverse events (Table 8.1). For example, individuals receiving fluvastatin (OR: 0.59, 95% CrI: 0.36, 0.95) and atorvastatin (OR: 0.66, 95% CrI: 0.48, 0.94) had lower odds of experiencing major coronary events as compared to those receiving rosuvastatin. Individuals randomized to rosuvastatin were also more likely to discontinue treatment due to experiencing adverse events as compared to those receiving pravastatin (OR: 1.45, 95% CrI: 1.06, 1.96 – the reciprocal of this finding is reported in Table 1) and simvastatin (OR: 1.31, 95% CrI: 1.00, 1.73). There was statistical evidence that atorvastatin was less tolerable than other statins: individuals receiving atorvastatin had higher odds of discontinuing treatment due to adverse events as compared to those receiving pravastatin (OR: 1.46, 95% CrI: 1.11, 1.92) and simvastatin (OR: 1.32, 95% CrI: 1.05, 1.68).

Considering these findings in terms of ranking probabilities, fluvastatin had the most favorable efficacy profile followed by atorvastatin based on the available evidence on major coronary events (Figure 8.2): fluvastatin and atorvastatin had the highest probability of ranking best and second best treatments, respectively. This reflected the statistically detectable differences among individual statins, favoring atorvastatin and fluvastatin at comparable doses (Table 8.1). Unsurprisingly, the findings suggested that control treatment had the highest probability of ranking last in terms of its effect in reducing major coronary events. While pravastatin and simvastatin had the most favorable tolerability profile among statins, i.e., had the highest probability of ranking best in terms of their effect on discontinuations due to adverse events, atorvastatin and rosuvastatin had similarly high probabilities of ranking last on this outcome.

Taking into account additional outcomes complicate the therapeutic considerations for choosing among different options, as individual statins differ in terms of their comparative effects on different benefit and harm outcomes. For example, trial participants randomized to fluvastatin appeared to experience numerically fewer major cerebrovascular events as compared to those randomized to other statins although this finding was not statistically significant (Table 8.1). While fluvastatin performed worse than pravastatin (OR: 5.19, 95% CrI: 1.75, 16.70), rosuvastatin (OR: 3.25, 95% CrI: 1.08, 10.50), and simvastatin (OR: 4.50, 95% CrI: 1.49, 14.20) in terms of hepatic transaminase elevations, it performed better than

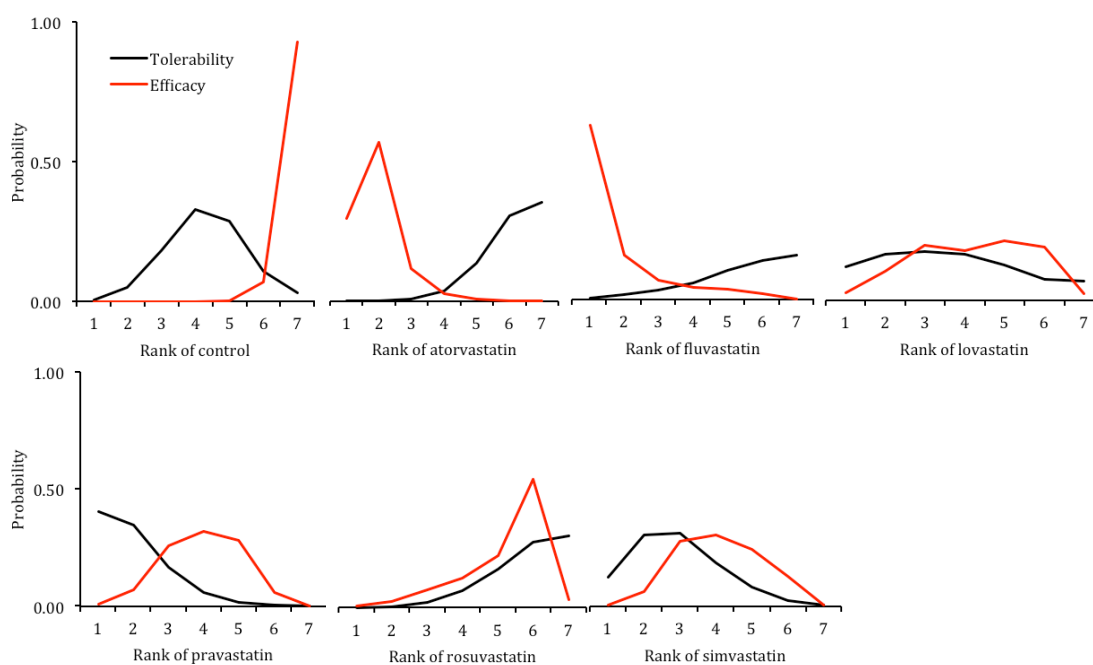
atorvastatin (OR: 0.18, 95% CrI: 0.04, 0.82 – the reciprocal of this finding is reported in Table 8.1), pravastatin (OR: 0.20, 95% CrI: 0.04, 0.88), rosuvastatin (OR: 0.18, 95% CrI: 0.04, 0.81), and simvastatin (OR: 0.20, 95% CrI: 0.04, 0.94) in terms of creatine kinase elevations. Finally, individuals receiving atorvastatin had higher odds of experiencing hepatic transaminase elevations than those receiving pravastatin (OR: 2.55, 95% CrI: 1.54, 4.14), rosuvastatin (OR: 1.60, 95% CrI: 1.06, 2.38), and simvastatin (OR: 2.20, 95% CrI: 1.36, 3.52).

**Table 8.1** – Comparative benefits and harms of individual statins according to network meta-analyses across all populations.\*

	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin	Outcome	Outcome
Atorvastatin vs.	1.11 (0.42, 2.79)	0.78 (0.52, 1.14)	0.91 (0.72, 1.11)	0.85 (0.64, 1.07)	0.99 (0.73, 1.28)	Total mortality	Benefit
	1.13 (0.70, 1.85)	0.83 (0.57, 1.16)	0.82 (0.65, 1.11)	0.66 (0.48, 0.94)	0.83 (0.58, 1.10)	Major coronary events	
	1.45 (0.32, 7.14)	1.07 (0.56, 1.98)	0.87 (0.64, 1.20)	0.87 (0.64, 1.20)	1.05 (0.79, 1.47)	Major cerebrovascular events	
	0.95 (0.63, 1.45)	1.24 (0.84, 1.87)	1.46 (1.11, 1.92)	1.01 (0.82, 1.25)	1.32 (1.05, 1.68)	Discontinuations due to adverse events	Harm
	1.08 (0.56, 2.17)	0.87 (0.54, 1.46)	1.10 (0.77, 1.53)	0.88 (0.71, 1.08)	1.28 (0.88, 1.80)	Myalgia	
	0.49 (0.15, 1.42)	1.26 (0.57, 2.73)	2.55 (1.54, 4.14)	1.60 (1.06, 2.38)	2.20 (1.36, 3.52)	Transaminase elevations	
Fluvastatin vs.		1.32 (0.54, 2.88)	1.13 (0.65, 1.78)	0.99 (0.64, 1.53)	1.13 (0.65, 1.97)	Creatine kinase elevations	Benefit
		0.71 (0.26, 1.87)	0.82 (0.33, 2.13)	0.76 (0.30, 2.00)	0.89 (0.34, 2.32)	Total mortality	
		0.74 (0.42, 1.20)	0.73 (0.48, 1.16)	0.59 (0.36, 0.95)	0.74 (0.43, 1.15)	Major coronary events	
		0.73 (0.13, 3.68)	0.61 (0.12, 2.73)	0.60 (0.12, 2.67)	0.74 (0.15, 3.33)	Major cerebrovascular events	Harm
		1.30 (0.81, 2.10)	1.53 (0.98, 2.34)	1.06 (0.68, 1.63)	1.39 (0.88, 2.14)	Discontinuations due to adverse events	
		0.81 (0.37, 1.71)	1.02 (0.48, 2.02)	0.82 (0.40, 1.58)	1.19 (0.56, 2.37)	Myalgia	
Lovastatin vs.		2.58 (0.76, 9.03)	5.19 (1.75, 16.7)	3.25 (1.08, 10.5)	4.50 (1.49, 14.2)	Transaminase elevations	Benefit
		0.24 (0.05, 1.17)	0.20 (0.04, 0.88)	0.18 (0.04, 0.81)	0.20 (0.04, 0.94)	Creatine kinase elevations	
			1.16 (0.80, 1.68)	1.08 (0.73, 1.61)	1.26 (0.84, 1.89)	Total mortality	
			0.99 (0.74, 1.47)	0.79 (0.56, 1.22)	1.00 (0.69, 1.38)	Major coronary events	Harm
			0.81 (0.46, 1.49)	0.82 (0.43, 1.55)	0.99 (0.54, 1.86)	Major cerebrovascular events	
			1.17 (0.77, 1.78)	0.81 (0.53, 1.25)	1.06 (0.69, 1.63)	Discontinuations due to adverse events	
Pravastatin vs.			1.26 (0.70, 2.15)	1.00 (0.58, 1.68)	1.46 (0.80, 2.54)	Myalgia	
			2.03 (0.90, 4.56)	1.27 (0.55, 2.93)	1.76 (0.75, 4.12)	Transaminase elevations	Benefit
			0.84 (0.39, 1.94)	0.76 (0.34, 1.85)	0.86 (0.37, 2.23)	Creatine kinase elevations	
				0.93 (0.75, 1.17)	1.08 (0.85, 1.39)	Total mortality	
				0.81 (0.58, 1.04)	1.02 (0.68, 1.24)	Major coronary events	Harm
				1.00 (0.75, 1.30)	1.21 (0.94, 1.57)	Major cerebrovascular events	
Rosuvastatin vs.				0.69 (0.51, 0.94)	0.91 (0.67, 1.24)	Discontinuations due to adverse events	
				0.80 (0.55, 1.19)	1.17 (0.74, 1.82)	Myalgia	Harm
				0.63 (0.36, 1.10)	0.87 (0.47, 1.57)	Transaminase elevations	
				0.89 (0.51, 1.63)	1.01 (0.55, 2.00)	Creatine kinase elevations	
					1.16 (0.88, 1.53)	Total mortality	Benefit
					1.27 (0.82, 1.67)	Major coronary events	
Rosuvastatin vs.					1.21 (0.88, 1.69)	Major cerebrovascular events	Benefit
					1.31 (1.00, 1.73)	Discontinuations due to adverse events	
					1.46 (0.98, 2.14)	Myalgia	
					1.38 (0.79, 2.38)	Transaminase elevations	Harm
					1.14 (0.62, 2.19)	Creatine kinase elevations	

\* Estimates shown are ORs and 95% CIs, as previously presented in Chapters 5 and 6. Table should be read from left to right.

**Figure 8.2** – Distribution of ranking probabilities for individual statins for major coronary events and discontinuations due to adverse events.\*



\* Ranking for each treatment indicates the probability to be the best treatment, the second best, the third best, and so on. For simplicity, this figure provides the relative ranking probabilities for only two outcomes. Tolerability depicts discontinuations due to adverse events whereas efficacy refers to primary and secondary prevention of major coronary events.

Given the difficulty in interpreting the findings from multiple network meta-analyses on several benefit and harm outcomes, Table 8.2 shows the overall ranking of individual statins for each benefit and harm outcome.

**Table 8.2** – Overall ranking of individual statins by their probability to be the best treatment in terms of benefit and harm outcomes.\*

	Atorva	Fluva	Lova	Prava	Rosuva	Simva
All-cause mortality	3	<b>1</b>	6	4	5	2
Major coronary events	2	<b>1</b>	5	4	6	3
Major cerebrovascular events	4	2	3	5	6	<b>1</b>
Discontinuations due to adverse events	6	5	3	<b>1</b>	4	2
Myalgia	4	2	5	3	6	<b>1</b>
Transaminase elevations	5	6	4	<b>1</b>	3	2
Creatine kinase elevations	6	<b>1</b>	2	3	5	4

\* Atorva: atorvastatin; Fluva: fluvastatin; Lova: lovastatin; Prava: pravastatin; Rosuva: rosuvastatin; Simva: simvastatin.

Figure 8.3 presents the combined benefit and harm profiles of individual statins where the ranking probabilities for individual statins on different outcomes are summarized into a single number (surface under the cumulative ranking line, SUCRA),<sup>324</sup> showing the contribution of each outcome to the overall benefit and harm score for each statin. According to this figure, fluvastatin ranked first in terms of its clinical efficacy with an overall score of 0.83 out of 1.00, followed by atorvastatin with 0.71, and simvastatin with 0.65. When ranked on the basis of combined harm outcomes, pravastatin (0.71) and simvastatin (0.70) appeared to perform better than other statins.

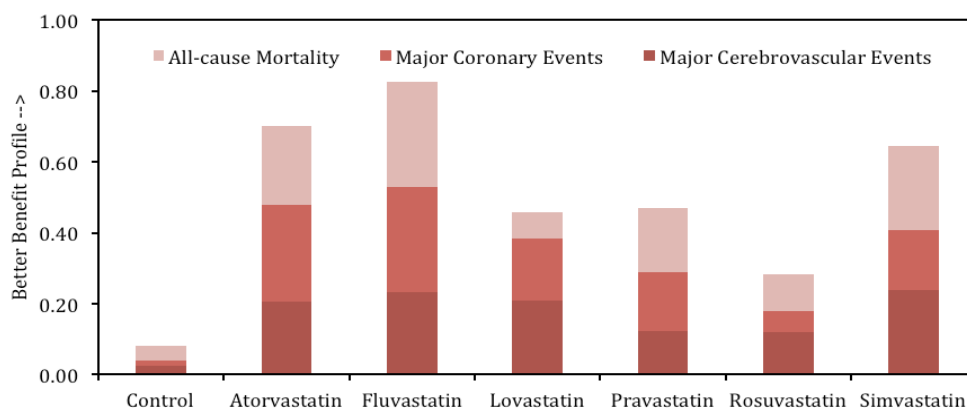
Putting both benefit and harm outcomes together, Figure 8.4 shows the overall comparative benefit and harm profiles of six statins where the size of each circle is proportional to the number of randomized participants included in the published placebo-controlled and active-comparator trials of statins. According to this figure, simvastatin appeared to have the most favorable benefit-harm profile: although both fluvastatin and atorvastatin had higher combined benefit scores, simvastatin had a considerably higher combined harm score (Figure 8.4). This figure also highlights the paucity of available data on some statins. In particular, considerably fewer individuals received fluvastatin and lovastatin as compared to other statins.

An important limitation of summarizing the empirical findings of the previous chapters as presented in Figure 8.4 is the underlying assumption that all benefit and harm outcomes are

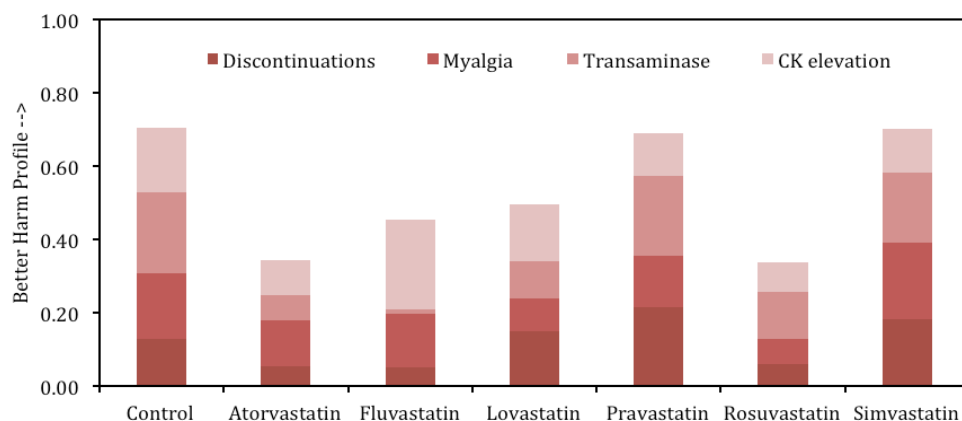
equally important, and hence contribute equally to the combined benefit and harm scores. Considering the types of outcomes evaluated in the network meta-analyses (ranging from minor reversible liver enzyme irregularities to deaths), this assumption does not hold. It is possible that prescribers initiating statin therapy in individuals with high cholesterol levels would consider long-term benefits to be more important than short-to-intermediate term harms. As such, prescribers may select fluvastatin given its favorable benefit score for long-term benefits. Alternatively, prescribers prioritizing harm outcomes (for example among frail elderly patients) may prefer pravastatin given its favorable harm profile.

**Figure 8.3** – Overall ranking of individual statins by their probability to be the best treatment in terms of benefit and harm outcomes.\*

**(A)**

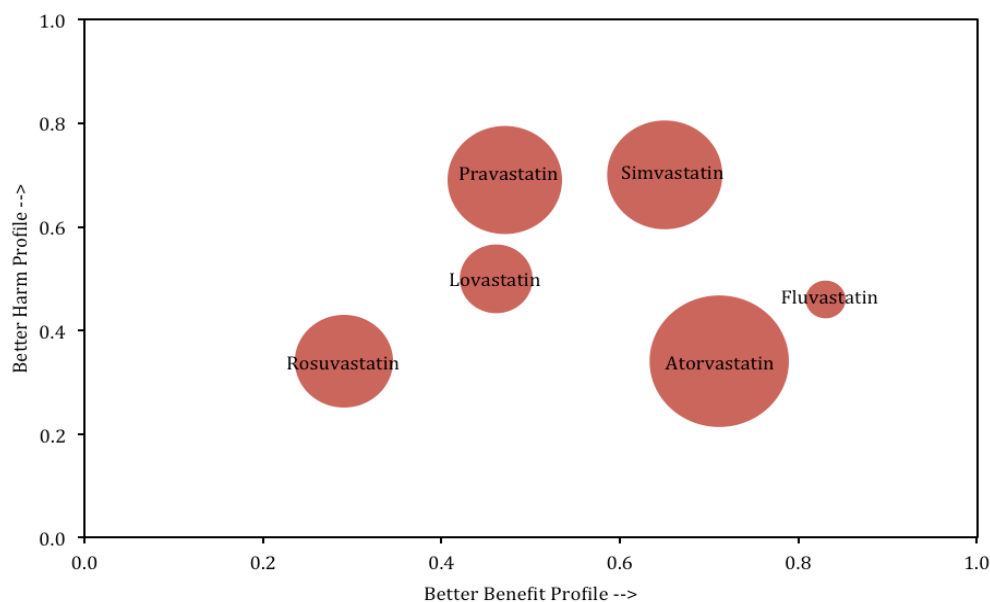


**(B)**



\* (A) all-cause mortality, major coronary events, and major cerebrovascular events, and (B) discontinuations due to adverse events, myalgia, transaminase elevations, and creatine kinase elevations. Each statin was scored with points up to a maximum of 1.00, with higher scores indicating better benefit and harm profiles, taking into account the magnitude and uncertainty of the cumulative probability of being the best treatment. Each benefit outcome contributed 1/3 of the total benefit score, and each harm outcome contributed 1/4 of the total harm score.

**Figure 8.4** – Comparative benefit-harm profiles of individual statins on the basis of placebo-controlled and active-comparator trials.\*



\* The figure combines the overall benefit (all-cause mortality, major coronary events, and major cerebrovascular events) and harm (discontinuations due to adverse events, myalgia, transaminase elevation, and creatine kinase elevation) scores for each statin estimated based on cumulative probabilities of being the best treatment. The size of each circle is proportional to the number of randomized participants according to the systematic review of published placebo-controlled and active-comparator trials of statins.

Insofar as the systematic review and network meta-analysis reported in this thesis provided much-needed answers regarding the comparative effects of individual statins, it also highlighted the challenging nature of making sense of the existing evidence on harms and benefits of multiple alternatives, and their trade-offs. Although it provided evidence of the benefits and harms comparatively, synthesizing a large volume of complex information, this comprehensive review did not conclusively distinguish between individual statins, complicating the decision around which statin should be preferred as the first drug of choice in clinical practice, and underscoring the challenges facing prescribers who are charged with basing their decisions on this body of evidence. Compounding this problem, there was no clear winner among statins (i.e., no statin outperformed its competitors in terms of both benefit and harm outcomes), leaving it up to the prescriber to decide whether – and to what extent – long-term clinical benefits seemed to outweigh more intermediate-term harms for any given statin.

The complexity of prescription drug therapy stems from the difficulty in making trade-offs between the benefits and harms of two or more options. Frustrating for prescribers, there is a lack of a conceptual framework with regard to balancing the benefits and harms of

prescription drugs. Increasingly, however, researchers are turning to multi-criteria decision analysis for these kinds of decision problems,<sup>476</sup> which is a formal framework for analysis of complex decision problems involving trade-offs between multiple outcomes.<sup>477</sup> An attractive feature of multi-criteria decision analysis is that it applies qualitative preferences on different outcomes, allowing for a transparent judgment on their relative importance.<sup>478,479</sup>

Combining network meta-analysis with multi-criteria decision analysis could potentially greatly improve the interpretability of existing evidence by making explicit the difficult trade-offs between outcomes. When applied to prescription drug therapy, multi-criteria decision analysis consists of four key elements.<sup>477</sup> First is choosing the alternatives to be appraised (e.g., multiple drugs in a given class). Second is deciding on the criteria against which the alternatives are appraised (e.g., different benefit and harm outcomes). Third is estimating the comparative performance of each alternative on each criterion (e.g., comparative effects of each drug on different benefit and harm outcomes). Finally, fourth is determining the criteria weights that indicate the relative values of each criterion as compared to others (e.g., preferences about the relative importance of different benefit and harm outcomes).

An important advantage of potentially combining network meta-analysis with multi-criteria decision analysis is that this combined approach would allow prescribers to weight different outcomes differently and see how drug rankings change according to individual preferences. Such explicit trade-offs would be necessary when incorporating the empirical findings of this thesis to clinical practice guidelines, thereby translating the current best evidence to high-quality prescribing decisions in clinical practice. First, clinical practice guideline developers may consider incorporating the findings of this systematic review and network meta-analysis alongside multi-criteria decision-analysis to make explicit trade-offs between multiple clinical benefit and harm outcomes.<sup>486</sup> Second, the summary of the existing clinical literature on statins can be combined with prescriber knowledge and patient preferences at point-of-care settings when making prescribing decisions. For example this might take the form of a decision support tool that relies on the findings of published network meta-analyses, which can then be considered in light of user knowledge and preferences.<sup>487</sup> A key advantage of this approach would be that preferences used to determine the relative importance of different benefit and harm outcomes can reflect those of patients.<sup>488</sup> Considering patient values would facilitate shared decision-making between patients and prescribers in choosing among multiple drugs.

### **8.5 Generalizability of Findings: To Whom Do the Results Apply?**

Another important consideration for prescribers is deciding whether (and to what extent) the findings of this review apply to individuals in clinical practice, and if so, which groups of

individuals. Generalizability of the findings of the network meta-analysis depends on the external validity of the individual randomized controlled trials included in the analysis. External validity is the relevance of a trial's results to clinical practice and the confidence with which the results from a specific trial population can be applied to other populations and settings.<sup>489</sup> For instance, there is concern that older adults enrolled in clinical trials may not be representative of the general population of older adults, potentially limiting the application of the findings to broader categories of patients. This is primarily attributed to the co-morbid conditions and the burden of multiple other medications in older adults.<sup>49</sup> However, due to the comprehensive nature of the systematic review that forms the basis of the network meta-analysis presented in this thesis, the findings would be expected to be generalizable to the majority of patients in clinical practice. This review included a broad range of patients and the benefits of statins appeared consistent in studies with populations that varied in age, geographic region, and severity of underlying illness, which adds to the strength of the overall inferences.

From a clinical standpoint, pre-defined inclusion and exclusion criteria ensured that the trials identified in the review (and included in the statistical analysis) were comparable in terms of important baseline characteristics. Given the continuous relationship between cholesterol concentrations and coronary heart disease risk, no definite threshold exists above which patients must be treated – and the decision to treat “high” cholesterol levels depends more on the expected risk reduction. As a result, there were potential differences across patient populations included in the network meta-analysis. Randomized trials varied considerably in terms of entry criteria and patients differed in terms of their co-morbidity profiles. Including trials with variable patient populations was justified on the grounds that the benefits of statins are consistent across a wide range of populations with diverse risk profiles. For instance, the largest randomized trial ever conducted on statins, the Medical Research Council/British Heart Foundation Heart Protection Study (HPS), which included over 10,000 individuals, showed that the benefits of statins extended to a wide range of patients at risk from cardiovascular events, including those with peripheral vascular disease, cerebrovascular disease, diabetes, and hypertension, with no detectable differences between different age groups and genders.<sup>139</sup>

Similar to previous reviews, the network meta-analysis presented in this thesis did not differentiate between individuals with and without diabetes (no separate sub-group analyses were conducted for groups of individuals with and without diabetes). Diabetes is considered as a coronary heart disease risk equivalent.<sup>154</sup> The risk of myocardial infarction in patients with diabetes without a history of myocardial infarction is as high as that in patients without diabetes who have had a myocardial infarction. The meta-analysis by Costa and colleagues showed that (in trials with at least three years of follow-up) reductions in

LDL cholesterol concentrations resulted in a significant decrease in the risk for major coronary events in diabetic patients.<sup>244</sup> There were similar relative risk reductions for major coronary events in both diabetic and non-diabetic patients for both primary and secondary prevention. Confirming these findings, a prospective individual patient-level meta-analysis performed by the Cholesterol Treatment Trialists showed that the proportional effects of statin therapy on each of the fatal and non-fatal clinical outcomes were similar for individuals with or without diabetes.<sup>245</sup> Taken together, these findings justified the inclusion of diabetic populations in the network meta-analysis.

Similarly warranted was the inclusion of trials with hypertensive patient populations. There is considerable evidence that high blood pressure and high cholesterol levels are clinically interrelated.<sup>490</sup> The association of high blood pressure and high cholesterol levels confers a greater increase in coronary heart disease risk than would be expected with either risk factor alone.<sup>491</sup> The meta-analysis by Messerli and colleagues showed that patients receiving statins had statistically significantly lower rates of cardiac events compared with patients in the control groups, and that hypertensive and non-hypertensive individuals conferred similar benefit from statin treatment.<sup>243</sup> Similar results were obtained in the individual patient-level analysis performed by the Cholesterol Treatment Trialists.<sup>175</sup>

While the patient populations included in the network meta-analysis were representative of a diverse range of patient populations, generalizing treatment options to individual patients seen in clinical practice remains a challenge. The primary consideration is that the findings of randomized controlled trials – or their syntheses in meta-analyses – are particularly helpful for the “average” patient or population. Since patients do not respond uniformly to therapies, a treatment that works on average in randomized controlled trials might not be relevant for every patient due to potential differences in terms of racial, ethnic, genetic, and environmental factors.<sup>492</sup> Despite much enthusiasm for tailoring decisions for individual patients, however, existing clinical evidence is not “granular” enough to individualize treatment options. Given the absence of adequate data on sub-groups by racial, ethnic, and genetic characteristics of patients, a synthesis of randomized controlled trials – as has been undertaken in this thesis – constitute the current best evidence on the comparative benefits and harms of statins, and should be used as a basis for making prescribing decisions about the care of individual patients.<sup>99</sup>

## Chapter 9

### Future Research Directions, Policy Implications, and Conclusions\*

Statins are among the most widely prescribed classes of drugs, used to prolong survival and reduce the risk of deaths, heart attacks, strokes, and other coronary events.<sup>220,238,493,494</sup> In addition to their favorable clinical effects, statins are also generally safe with regards to rare adverse events.<sup>381,382</sup> Although a large number of published randomized controlled trials compared statins head-to-head, findings of these active-comparator trials were neither systematically identified nor combined with the findings of placebo-controlled trials. Previous meta-analyses were pair-wise in nature, i.e., compared two treatments at a time (e.g., atorvastatin vs. placebo). As discussed in Chapter 3 (*Evidence Review and Synthesis Methods*), traditional pair-wise meta-analysis is incapable of comparing multiple treatments simultaneously.<sup>95</sup> Even previous attempts at analyzing the comparative benefits and harms of multiple statins did not identify and include active-comparator trials.<sup>105,214,348,359,392</sup> Thus, over the quarter century history of statins, there has not been any comprehensive review of the existing literature evaluating whether – and to what extent – individual statins at comparable doses (with similar LDL cholesterol lowering effects) are interchangeable in terms of their benefit and harm profiles.

Although the systematic review and network meta-analysis provides comprehensive evidence on the comparative benefits and harms of individual statins, as with any research endeavor, the empirical work presented in this thesis constitutes an unfinished research agenda. Future research directions are several, and include further investigating the potential mechanisms underpinning the observed comparative effectiveness of individual statins; exploring how best to incorporate patient preferences into statin prescribing decisions in clinical practice; and developing a framework for future evaluations of industry sponsorship bias in cardiovascular diseases and beyond.

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\* Part of the contents of this chapter has been published with the following reference: Naci H, O'Connor AB. Assessing comparative effectiveness of new drugs before approval using prospective network meta-analyses. *J Clin Epidemiol*. 2013 Aug;66(8):812-6.

## 9.1 Future Research Directions

A number of questions about the comparative benefits of individual statins remain unanswered. First, the observed effects of statins on all-cause mortality, major coronary events, and major cerebrovascular events (as reported in Chapter 5: *Comparative Benefits of Individual Statins*) are not entirely commensurate with their LDL cholesterol-lowering effects, suggesting that mechanisms beyond cholesterol-lowering may be responsible for the cardiovascular risk reduction associated with statin therapy. Supporting this view, other products (such as ezetimibe) that successfully lower LDL cholesterol have failed to convincingly reduce the risk of all-cause mortality, major coronary events, and major cerebrovascular events.<sup>495-498</sup>

Researchers have previously suggested that statins have pleiotropic effects beyond their LDL cholesterol lowering effects.<sup>499-501</sup> Based on a review of the experimental literature on the antiatherosclerotic and antithrombotic effects of fluvastatin, for example, Corsini concluded that the effects of fluvastatin may extend beyond cholesterol lowering.<sup>502</sup> In addition, a recent meta-analysis by Broekholdt and colleagues showed that non-HDL cholesterol had a more important role than LDL cholesterol in preventing the risk for cardiovascular events.<sup>347</sup> In a similar fashion, emerging evidence suggests that statins have anti-inflammatory effects that may be partially responsible for their efficacy in preventing coronary heart disease.<sup>503-505</sup> Whether these potential pleiotropic and anti-inflammatory effects – and cholesterol lowering effects that extend beyond LDL – are responsible for the finding that less potent statins are equivalent or better than more potent alternatives needs further examination. Potential future research opportunities include exploring the comparative anti-inflammatory, antithrombotic, and non-HDL-lowering effects of individual statins and investigating the relationship between these factors and cardiovascular disease risk.

Similarly, further investigation is warranted on the comparative harms of individual statins. For each of the tolerability and harm outcomes that were evaluated in Chapter 6 (*Comparative Harms of Individual Statins*), information was available in less than half of all randomized participants across all randomized controlled trials of statins. This is consistent with other therapeutic areas where reporting of harmful adverse events remains stubbornly inadequate.<sup>506,507</sup> In addition, outcomes in each trial were extracted as they were originally reported in the published accounts of the trials (i.e., as defined by trial investigators), which potentially introduced variability in outcome definitions. To build upon the empirical work presented in Chapter 6, an important research opportunity, devised in collaboration with Dr. John P. Ioannidis of Stanford University, is to seek individual patient-level data on standardized tolerability and harm outcomes from the investigators of all identified placebo-

controlled and active-comparator trials of statins reporting tolerability and harm outcomes. Performing more detailed network meta-analyses using individual patient-level data would yield new insights about the comparative harms of individual statins, with the possibility to explore additional outcomes, such as acute kidney injury associated with statin therapy,<sup>380</sup> that were rarely reported in the published literature.

Using individual patient-level data would have additional benefits,<sup>508</sup> particularly to evaluate whether patient-level characteristics, such as different comorbidity profiles, are related to statin efficacy.<sup>509</sup> Previous studies have shown that incorporating individual patient-level data into network meta-analyses produces markedly more accurate treatment-covariate interaction estimates than an analysis using aggregate study-level data alone.<sup>470</sup> Methods exist to synthesize both individual patient-level and aggregate study-level data, allowing for an exploration of potential relative treatment effect modifiers that are available in a combination of individual patient-level and study-level aggregate data.<sup>510</sup> Using individual patient-level data would also facilitate a more standardized analysis of outcomes. The majority of the included statin trials reported their results as composite endpoints. Although composite end points increased the event rate and thus the statistical power of trial results, they have previously been criticized as they may provide misleading information if component end points are of widely differing importance to patients, and the magnitude of effect differs markedly across components.<sup>467-469</sup> Given the paucity of more granular outcome information in the published accounts of randomized controlled trials, a careful examination of disaggregated endpoints (e.g., fatal vs. non-fatal myocardial infarctions) would be possible with access to individual patient-level data.

Another future research opportunity relates to the important yet largely unfulfilled promise of evidence-based prescribing. As highlighted throughout this thesis, prescribing decisions are complex and incorporating scientific evidence into such decisions remains challenging. Even in cases when comparative evidence on drugs exists, prescribers and patients often struggle to weigh the relative benefits and harms of multiple alternatives. As discussed in Chapter 8 (*Evidence-Based Decision-Making: Going from Evidence to Prescribing*), there is an opportunity to adopt a more formal framework to help prescribers and patients in identifying a first line drug among multiple alternatives. One option is to adopt decision analysis methods to encourage and facilitate shared decision making between prescribers and patients, by specifically combining network meta-analysis and multi-criteria decision analysis. However, considerable research is required before this vision can become reality. Important questions that remain unanswered are several, and include: Can patients reliably distinguish between different outcomes? What is the best forum for sharing the findings of network meta-analyses with patients (e.g., decision support tools, online education portals, printed materials)? What is the ideal setting to engage patients and seek their preferences

about different outcomes (e.g., clinical practice, home, other community setting)? Combining network meta-analysis and multi-criteria decision analysis would also allow for the incorporation of additional considerations that would influence the interpretation of existing evidence. For example, one possibility would be to put less weight on the treatments that have only minimal evidence.

Finally, findings of Chapter 7 (*Methodological Quality and Risk of Bias in Randomized Controlled Trials of Statins*) highlight the need for further research into the empirical basis for industry sponsorship biases, and the importance of adopting study designs, such as network meta-analysis, which are capable of distinguishing between industry sponsorship bias and actual differences between treatments and doses. For the analyses presented in Chapter 7 of this thesis, statins provided an excellent case study to explore industry sponsorship bias: all six statins are manufactured by competing pharmaceutical companies and each company conducted head-to-head trials of their products against alternative agents sponsored by other companies. As empirically shown in Chapter 4 (*Dose-Comparative Effects of Individual Statins*), there are actual differences in the effectiveness of individual statins that, when taken into account, explain previous findings of industry sponsorship bias. Future empirical evaluations should investigate the validity of previously observed associations between industry sponsorship and study findings and conclusions in other therapeutic areas. The particular mechanisms underlying the phenomenon of sponsorship bias needs further research. One such possibility would be to put less weight on treatment options that have relatively minimal evidence as compared to their alternatives, which might reflect a biased research agenda.

## **9.2 Policy Implications**

In the absence of comparative evidence, marketing claims have historically driven statin prescriptions – with sales of five statins trailing behind those of atorvastatin (Lipitor®, Pfizer). In recent years, Pfizer’s continued marketing efforts on atorvastatin despite cheaper generic competition helped it become the best-selling medication in history.<sup>511</sup> Indeed, atorvastatin in its brand formulation is the most commercially successful drug of all time in terms of peak annual performance, lifetime sales, and cumulative sales during the first 10 years of availability.<sup>512</sup> Over the course of its lifetime, atorvastatin has generated global sales of almost \$150 billion.<sup>513</sup> Between 2004 and 2010, it was the best selling medication in the US in terms of the number of units sold.<sup>514</sup> In 2010, its sales in the United States totaled \$7.2 billion.<sup>515</sup>

Even by the pharmaceutical industry’s standards, Pfizer’s marketing strategy has been exceptional in its scope and magnitude, making atorvastatin a blockbuster statin shortly

after its market entry. As reported by the USA Today in 2011 before atorvastatin lost its patent protection:<sup>516</sup>

Pfizer spent tens of millions of dollars on sales and marketing efforts, including on the popular drama "ER," first urging patients to "Know Your Numbers" and then showing patients discussing how Lipitor helped them get their cholesterol numbers below guideline goals. The Lipitor promotion team set new standards for a marketing campaign. They repeatedly visited family doctors as well as cardiologists, and blanketed patients with data showing that Lipitor was best at lowering cholesterol. They stressed to doctors nervous about safety that Lipitor's lowest dose worked as well as rivals' highest doses. They gave free samples of the white pills and sometimes bought lunch for the office staff. In another savvy move, Lipitor was priced below rival drugs. The company continued research on Lipitor, through [2011] conducting more than 400 studies, costing roughly \$1 billion and including more than 80,000 patients. The studies have shown how Lipitor helped patients with heart problems, diabetes, stroke risk and other conditions, by preventing heart attacks and strokes and reducing plaque buildup in arteries.

What made the success story of atorvastatin even more remarkable was the wider context of the statin market over the past decade. Simvastatin (Zocor®, Merck), the second best-selling statin in the United States, lost patent protection and became generically available in mid-2006. What followed was the widespread adoption of incentives by insurers and pharmacy benefit managers to switch patients on atorvastatin to simvastatin.<sup>517</sup> This typically took the form of formulary design changes by moving atorvastatin to the highest copayment tier (with considerable cost sharing) and placing simvastatin to the lowest tier (with minimal cost sharing). Despite these incentive mechanisms put in place to deter atorvastatin prescribing, by the end of 2006, more than two-thirds of statins prescribed were still brands with atorvastatin leading the way, even though three generic statins were already available including simvastatin.<sup>517</sup> Until its market expiry in 2011, Pfizer continued to spend heavily to promoting atorvastatin on advertising in print, on television and online, which totaled a \$271.9 million yearly budget.<sup>518</sup> Following its patent expiry in 2011, atorvastatin sales were at \$7.7 billion globally.<sup>519</sup>

Are the historical statin prescribing trends – and atorvastatin's exceptional performance – evidence-based according to the empirical findings presented in previous chapters of this thesis? As Chapter 4 (*Dose-Comparative Effects of Individual Statins*) showed, when the totality of randomized controlled trial evidence base was taken into account, simvastatin and atorvastatin had similar cholesterol-lowering effects even at their highest doses. In addition, the effects of simvastatin and atorvastatin on clinically meaningful benefit outcomes were similar with no statistically detectable differences in various network meta-analyses presented in Chapter 5 (*Comparative Benefits of Individual Statins*). However, as Chapter 6 showed (*Comparative Harms of Individual Statins*), simvastatin appeared to outperform atorvastatin in terms of tolerability and harm outcomes. Under alternative

scenarios where benefit and harm outcomes were combined and weighted using qualitative preference statements (Chapter 8: *Evidence-Based Decision-Making: Going from Evidence to Prescribing*), atorvastatin rarely surpassed other statins in terms of its comparative benefit and harm profile. In summary, atorvastatin's sales performance over the past decade was not based on the current best evidence according to the empirical findings presented in this thesis.

Clearly, and perhaps unsurprisingly, factors beyond comparative evidence motivated the historical statin prescribing patterns in the United States. The extent to which evidence influences prescribing decisions is difficult to assess as there is a wide array of competing factors underlying prescribing behavior. These include the effectiveness of pharmaceutical promotion practices,<sup>520</sup> and attractiveness of using newer drugs compared to those recommended as a result of scientific evidence so that prescribers are considered up-to-date.<sup>521</sup> Information overload is also an important factor, as prescribers find the current volume of scientific information unmanageable and instead rely on information provided by sales and marketing teams of pharmaceutical companies.<sup>42,53,522,523</sup> Also, regulatory mechanisms may play an indirect role in prescribing decisions.

An important consideration in generating comparative evidence is its timing. If the goal is to guide prescribing decisions, comparative effectiveness evidence needs to be generated prior to the widespread adoption of a drug. This is because once clinical practice is established; it may be particularly difficult to change prescribing patterns. For example, the federally funded 'Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial' (ALLHAT), which showed that older and cheaper antihypertensive drugs were as effective as their newer and more expensive alternatives, had only a modest impact on prescribing patterns.<sup>524</sup> Therefore comparative evidence that forms the basis of high quality prescribing decisions should be assembled early on – ideally at the drug approval stage. Currently, the United States Food and Drug Administration does not require the inclusion of statements regarding a drug's comparative effectiveness in product labels.<sup>525</sup> The current lack of consideration for comparative effectiveness evidence at the time of drug approval plays an indirect role in guiding prescribing decisions. Concomitant with Food and Drug Administration's approval to prescribe a new drug for an indication, drug manufacturers initiate a plethora of marketing campaigns to enhance the product awareness of prescribers. In the case of rosuvastatin (Crestor®), AstraZeneca launched an extensive marketing campaign immediately following market entry to promote the drug as the most potent statin available, which led to a debate about the dangers of widely promoting a drug with no safety record.<sup>526</sup>

### 9.3 An Opportunity for Regulatory Reform

The current regulatory environment constitutes an opportunity to raise the bar for market authorization of new drugs. One important component of potential regulatory reform is requiring comparative evidence at the time of drug approvals. Such a requirement would have significant benefits. As described in detail by Sorenson and colleagues,<sup>527</sup> evidence on the comparative benefits and harms of new drugs is needed by a range of decision makers upon market entry. Comparative evidence can help regulatory agencies to ensure that products that are inferior to existing alternatives are identified early on, allow third-party payers make coverage and reimbursement decisions based on the best available evidence on different treatment options, and aid prescribers and patients understand what therapies work best.

A related limitation of the existing regulatory framework for new drugs is that judgments of efficacy are often based on surrogate outcome measures, not clinical endpoints, which can complicate the assessment of benefits and harms at the time of market entry.<sup>528</sup> Use of surrogate endpoints may sometimes be warranted on the basis that they are strong predictors of long-term clinical outcomes.<sup>529</sup> Surrogate endpoints facilitate efficiency in the drug evaluation process by effectively reducing the size and duration of trials. For example, lowering LDL cholesterol levels strongly correlate with a reduction in coronary heart disease and mortality risk. However, surrogate endpoints can also yield findings that suggest benefit when no such effect in clinical outcomes exists. Recent years have revealed several problems with drugs evaluated and approved on the basis of surrogate measures alone. While some drugs were outright harmful (rosiglitazone, which was shown to cause cardiovascular events, was originally approved based on its ability to reduce short-term hemoglobin A1c levels in patients with diabetes),<sup>530</sup> others like ezetimibe failed to convincingly show evidence to reduce the risk of major coronary events and mortality despite evidence of cholesterol-lowering effects.<sup>495,496,498,531</sup> Thus, approving products on the basis of surrogate measures may not meet the information needs of prescribers.

Regulatory experts have recently called for requiring comparative evidence on clinically meaningful outcomes (e.g., mortality, heart attacks, strokes). Although an estimated half of new drugs approved in the United States over the last decade had some comparative efficacy data available at the time of market authorization,<sup>532</sup> there remains a paucity of meaningful comparative evidence available on clinical outcomes at the time of new drug approval and beyond. Even if comparative evidence for market approvals becomes the norm, the ultimate health impact of new therapies approved on the basis of surrogate endpoints may remain unknown until post-market evidence. In general, commentators have pushed for basing drug approvals on trials that measure clinical outcomes. Yet, despite calls to raise the bar for

market entry, previous licensing decisions appear to set a precedent in the regulatory setting: all six of the currently marketed statins were granted market authorization on the basis of their LDL cholesterol lowering effects as opposed to their effect on reducing the risk for clinical events. In the case of atorvastatin, for example, a regulatory comparison with simvastatin on mortality outcomes would have potentially shown the lack of superiority of this agent over simvastatin, and might have curbed some of the widespread enthusiasm that stemmed from Pfizer's subsequent sales and marketing efforts.

Although pharmaceutical companies are vehemently, and understandably, opposed to making comparative evidence on clinical outcomes the default evidentiary standard at the regulatory setting, raising the bar for market entry does not seem to have a negative impact on drug approval rates. In fact, since the 1962 regulatory requirement in the United States for pharmaceutical companies to establish evidence of safety and effectiveness, there has been an increase, rather than decrease in the number of products reaching the market over the long-run. An analysis by Munos showed that the rate of drug approvals has been constant over the past 60 years with a slight upward trend from the period 1980-1995 (culminating in 53 approvals in 1996).<sup>533</sup> Further, during a period where various aspects of regulatory expectations for evidence increased, the number of innovative drugs entering the United States market increased.<sup>534</sup> Indeed, as discussed by Naci and colleagues, raising the evidentiary threshold could guide pharmaceutical industry's priorities and encourage more efficient allocation of research investment.<sup>535</sup> By requiring comparative evidence for market entry, common sense dictates that pharmaceutical companies would be more likely to invest in therapeutic areas with few or no existing treatment options rather than investing in areas with existing alternatives.

Recent calls for reform at the Food and Drug Administration focused on the importance of active comparator trials for generating comparative evidence. However, there are considerable challenges to formally requiring these types of trials at the time of regulatory approvals.<sup>536</sup> Active comparator trials may be unfeasibly large and costly when multiple comparators are included – particularly when evidence on long-term clinical outcomes is required. Even if active comparator trials were required, it would not be possible to compare new drugs to all available alternatives (in the case of statins, this would require a randomized controlled trial with seven arms comparing all available statins to each other and to control). Nevertheless, the Food and Drug Administration is committed to emphasize the importance of active comparator trials and continue to collaborate with independent consultants to define the clinically relevant comparators, meaningful short- and long-term outcomes, dosing regimens, and margins of superiority, equivalence, and non-inferiority necessary in these study designs in cases where they are warranted, for example when there are only two drugs available in a class.<sup>537</sup> In cases where active-comparator trials are not

feasible to compare all available drugs in a given class, however, an alternative option is to establish a formal role for prospectively designed network meta-analysis before market entry. Prospectively designed network meta-analysis can be used to determine the comparative clinical benefit and harm profiles of drugs at the time of market authorization decisions.

#### **9.4 Obtaining Comparative Evidence Before Market Entry Using Prospective Network Meta-analysis**

Evidence review and synthesis methods such as meta-analyses are already used in the regulatory setting, for example to address essential safety questions.<sup>538</sup> In a recent case, a series of traditional pair-wise meta-analyses were pivotal in raising safety signals for rosiglitazone (Avandia®).<sup>539,540</sup> In the United States, these concerns also contributed to the Food and Drug Administration's 2008 Guidance for Industry on "Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes", which encourages manufacturers of new antidiabetic drugs to perform prospective traditional pair-wise meta-analyses to evaluate cardiovascular events associated with their products relative to control treatment and explore similarities and/or differences in subgroups.<sup>541</sup> As discussed in Chapter 3 (*Evidence Review and Synthesis Methods*), in conditions with several drug options, pair-wise meta-analysis is limited by the relatively small number (or the complete lack) of trials that directly compare a particular pair of drugs. By definition, pair-wise meta-analysis is incapable of comparing multiple active comparators simultaneously.

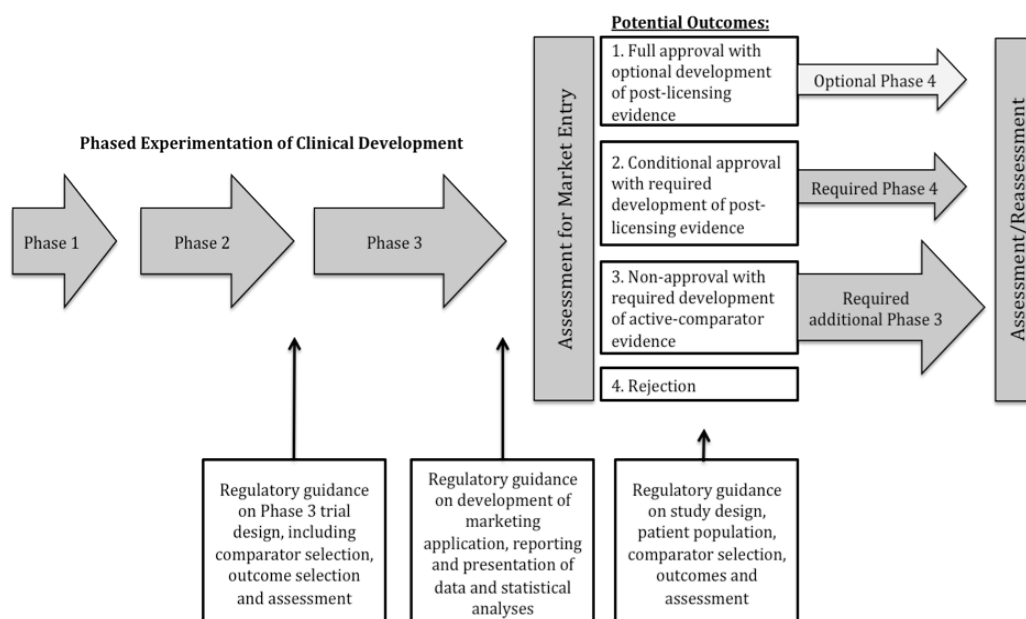
Unlike pair-wise meta-analysis, network meta-analysis is capable of evaluating the comparative benefits and harms of two or more drugs, even when the drugs are not directly compared to each other in randomized trials.<sup>97</sup> In the regulatory setting, network meta-analysis allowing the comparison of multiple drugs can help to estimate the benefit and harm profiles of new drugs relative to existing alternatives at the time of market entry before prescribing patterns are established. Specifically, network meta-analysis could be used as a basis for estimating effect sizes for clinical efficacy and safety endpoints during regulatory assessment for market authorization of new drugs.

A simplified overview of the current regulatory process for market authorization of new drugs is provided in Figure 9.1. There are three phases of experimentation prior to the regulatory assessment of new drugs for market entry.<sup>542</sup> In Phase 1, an investigational drug is tested in a small number of healthy volunteers to explore its safety profile in terms of toxicity. In Phase 2, tests are performed on a larger number of individuals with a given condition to assess whether the drug provides intended clinical benefits, and to monitor short-term side effects. In Phase 3, the drug is tested in a larger group of individuals with a

given condition to evaluate its clinical efficacy and safety. Regulatory assessment for market authorization follows the completion of Phase 3.

As shown in Figure 9.1, regulatory agencies are heavily involved in the clinical development of new drugs. In the case of the Food and Drug Administration, an “end-of-Phase 2 meeting” is arranged to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 trial plan and protocols and the adequacy of current studies, and to identify any additional information necessary to support regulatory assessment following the completion of Phase 3.<sup>543</sup> Following the completion of Phase 3, regulators and pharmaceutical companies have another opportunity to discuss a number of topics in regards to the marketing application, including the appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation of data in the marketing application.

**Figure 9.1** – A simplified overview of regulatory involvement during the phased experimentation of drug development and potential outcomes of market entry assessment.\*



\* Figure adapted from Naci H and O'Connor AB. Assessing the comparative effectiveness of new drugs using pre-planned network meta-analysis. *Journal of Clinical Epidemiology*. 2013 Aug;66(8):812-6.<sup>544</sup>

At the time of regulatory assessment for market authorization (following the completion of Phase 3 trials), network meta-analysis could be used to estimate the comparative efficacy and safety of the new drug and its existing alternatives. In cases where no active-comparator trials exist, network meta-analysis could generate estimates of comparative efficacy and safety. In cases where active-comparator trials exist, network meta-analysis could combine the findings of the direct comparisons with those from indirect comparisons for support of superiority, equivalence, or non-inferiority claims. In cases where only active-comparator trials exist, these could be combined in network meta-analysis as long as drugs are compared to each other in a network.

#### 9.4.1 *Network Meta-analysis and Market Authorization Decisions*

At the time of regulatory assessments for market entry, network meta-analysis could potentially suggest that a new drug is superior, equivalent, or inferior to one or more existing alternatives. Superiority could be determined via more beneficial (e.g., more efficacy at the primary endpoint) and/or less harmful effects (e.g., less discontinuation due to adverse events). Similarly, inferiority could be determined via less beneficial (e.g., less

efficacy at the primary endpoint) and/or more harmful effects (e.g., more discontinuations due to adverse events).

Prospectively designed network meta-analysis would offer important benefits at the regulatory setting. A prospective network meta-analysis can be defined as a meta-analysis of trials that are identified, evaluated and determined to be eligible for the meta-analysis before the results of any of those studies are known.<sup>549</sup> Phase 3 trials submitted to regulatory agencies for market authorization assessment could form the basis for performing network meta-analyses at the time of new drug approval.

The keys to performing network meta-analyses are having trials of comparable characteristics with similar patient populations (i.e., balanced distribution of relative treatment effect modifiers across treatment comparisons in the evidence network). The Food and Drug Administration could help emphasize the use of similar trial designs and patient populations for different drugs seeking approval for a shared indication in anticipation of future network meta-analysis. Whenever possible, trials for a specific indication can conform in terms of patient populations, outcomes, outcome assessment techniques, follow-up time points, and dosing regimens. In addition, regulators and pharmaceutical companies could work together to identify relative treatment effect modifiers to ensure that potential sources of heterogeneity can be explored across trials.

Regulatory agency involvement in the design of the trials would help minimize design and population differences between trials, reducing the risk for bias when comparing across trials by ensuring that trials are comparable in terms of relative treatment effect modifiers. Similar to current collaborative efforts in determining acceptable surrogate endpoints and time points for follow-up assessments of randomized trials, pharmaceutical companies and regulators could collaborate on pre-determining non-inferiority, equivalence, and superiority margins when two or more active comparators are evaluated in network meta-analyses.<sup>550</sup> Reaching consensus *a priori* on how to evaluate the balance between benefits and harms would be particularly important given the existing challenges in objectively quantifying side effects in relation to clinical effects, which form the basis of regulatory decisions.<sup>551</sup>

Having access to the individual patient-level data from the clinical trials would considerably strengthen the utility of network meta-analyses at the regulatory setting. In the case of the Food and Drug Administration, regulatory agency statisticians have access to all individual patient-level data from clinical trials, whether published or not, which include large, computerized dataset for each randomized controlled trial as well as its protocol and clinical study report. Although not required, network meta-analysis with individual patient-level data would be desirable when taking into account the distribution of relative treatment

effect modifiers across treatment comparisons.<sup>470</sup> Using data sources that are to a great extent not available to the wider public, regulators can perform their own analyses assessing the comparability of trials, sources of potential bias, and so forth. Accordingly, the Food and Drug Administration could then incorporate network meta-analysis results into its decision-making and into product labelling, helping to better inform the public about new treatments before treatment patterns are established. This would not only allow for performing comparative assessments at the regulatory level, but also facilitate downstream ‘after-approval’ evaluations of drugs by public and private insurers, and pharmacy benefit managers.

#### 9.4.2 *Challenges Ahead*

Planning future trials to inform future network meta-analyses would go against the current (*perceived*) practice of planning each individual trial in isolation from the others.<sup>538</sup> Although pharmaceutical companies may be understandably opposed to designing their trials to mirror those of their competitors, the Food and Drug Administration already provides comprehensive scientific guidance to ensure that separate trials submitted at different time points by different pharmaceutical companies are sufficiently comparable clinically to warrant the same indication. Given its current level of involvement, the Food and Drug Administration could play a greater role in guiding the design of Phase 3 trials to allow future network meta-analyses to be done. In attempts to arrive at a feasible approach, the Food and Drug Administration and pharmaceutical companies can continue collaborating on issues related to trial design, selection of appropriate comparators, and ensure that patient populations are as similar as possible across Phase 3 trials in terms of relative treatment effect modifiers.

Certain aspects of this proposal may require legislative action. At the moment, the Food and Drug Administration is not required to consider comparative evidence in its market authorization decisions. Although the European Medicines Agency is increasingly favoring the submission of comparative data for market entry considerations,<sup>552</sup> the Food and Drug Administration prefers to consider it on a case-by-case basis.<sup>553</sup> Further, the Food and Drug Administration may not be allowed to use individual patient-level data from the marketing application of one drug in the evaluation of another, which would prevent it from performing analyses with datasets that are not available to the research community. It is important to note, however, that the data access landscape is quickly changing with widespread enthusiasm to make individual patient-level data from randomized controlled trials of drugs available.<sup>554-557</sup> Such an approach would also have benefits for the pharmaceutical industry.<sup>558</sup> Acknowledging this potential, GlaxoSmithKline has made a commitment to release individual patient-level data from its clinical trials.<sup>559</sup>

## 9.5 Implications of Regulatory Reform for Market Authorization of Cholesterol-Lowering Drugs

In August 2009, the Food and Drug Administration approved pitavastatin (Livalo®) for the indication of cholesterol lowering, making it the seventh statin currently available for sale in the United States. As Gagne and Choudhry observed “This approval [came] almost a quarter century after that for the first member of the class, lovastatin, [eight] years after generic lovastatin was approved and [four] years after [two] additional statins, pravastatin and simvastatin, lost patent protection and generic versions of them entered the market.”<sup>560</sup> Pitavastatin was approved based on its non-inferior LDL cholesterol lowering ability compared with atorvastatin, simvastatin, and pravastatin. Four years after its market entry, information on whether – and the extent to which – pitavastatin lowers the risk of coronary and cerebrovascular events and deaths remains unknown. In a similar fashion, how pitavastatin fares against existing statins has not been evaluated.

If the potential regulatory reform proposed in this chapter was in place at the time of pitavastatin’s market entry, rather than approving pitavastatin on the basis of its cholesterol-lowering effects, the Food and Drug Administration could have required a large active-comparator non-inferiority trial evaluating the impact of pitavastatin on major coronary and cerebrovascular events as compared to a suitable competitor such as simvastatin. A non-inferiority trials could evaluate whether pitavastatin was not worse than an active control by more than a specified “non-inferiority” margin.<sup>545</sup> In contrast to superiority designs, non-inferiority designs require external information to confirm that the active control had its expected effect in the study (also termed assay sensitivity, which refers to the ability to distinguish an effective from an ineffective drug on the basis of its superiority to placebo).<sup>546</sup> Although assay sensitivity is achievable in non-inferiority trials with three arms (placebo and two active comparators), the use of placebo is no longer ethical in statin trials. In such scenarios, network meta-analysis can be particularly helpful. Regulators could determine the comparative benefit and harm profile of pitavastatin versus other statins using network meta-analysis.

Availability of comparative data is particularly relevant for the new class of powerful cholesterol-lowering drugs that are currently in the pharmaceutical research and development pipeline. Given the potential of these products (PCSK9 inhibitors) to lower cholesterol concentrations to levels not possible with statins, pharmaceutical companies are currently competing to bring them to market.<sup>561</sup> Sanofi and Regeneron Pharmaceuticals have recently reported the findings of their early-stage investigations<sup>562</sup> and have reportedly initiated a Phase 3 trial involving 18,000 patients with a recent heart attack or angina pectoris who cannot lower their cholesterol levels with statin therapy alone. Amgen has also

reported Phase 1 trial results and has begun Phase 3 trials.<sup>563</sup> Other companies with drugs in mid-stage clinical trials include Pfizer, Roche, Eli Lilly & Company, and Alnylam.

Regulatory involvement during this stage of clinical development, already underway, is essential to ensure that the trials designed by these pharmaceutical and biotechnology companies are adequately similar in terms of important relative treatment effect modifiers to allow for their combination in future network meta-analyses. Important considerations include the use of similar comparator groups (e.g., simvastatin at 20mg/day); patient populations (e.g., individuals with established coronary heart disease, secondary prevention); and clinical endpoints (e.g., major coronary and cerebrovascular events and deaths).

Regulatory agency involvement might help to avert a highly undesirable – yet all too likely – scenario whereby pharmaceutical companies that are currently developing PCSK9 inhibitors separately conduct clinical trials on slightly different populations and use different comparator groups, which might not allow for a credible comparison of their products' comparative efficacy and safety. Lack of comparative evidence would leave prescribers in the dark about the comparative benefits and harms of this new class of therapies relative to statins, and once again create a significant information gap for evidence-based decision-making in clinical practice, setting off yet another marketing race among pharmaceutical companies.

## **9.6 Conclusion**

Comparative data on clinically meaningful benefit and harm outcomes is critical to ensure evidence-based prescribing decisions in clinical practice. Despite their limitations, the empirical findings presented in this thesis provide the most comprehensive assessment of the comparative benefit and harm profiles of individual statins to guide high-quality prescribing decisions. Using 184 randomized controlled trials including 260,630 individuals with or without cardiovascular disease, this thesis made four major contributions to the literature on the comparative effectiveness and safety of individual statins, showing the following: (1) cholesterol-lowering effects of statins are less pronounced than suggested by the previous reviews focusing on small placebo-controlled trials alone; (2) individual statins potentially differ in terms of their comparative effects on clinically meaningful outcomes such as all-cause mortality, major coronary events, and major cerebrovascular events, with less potent statins performing equally well with those capable of achieving more LDL cholesterol reductions per mg dose; (3) harms associated with statins are rare; but some statins such as simvastatin and pravastatin are safer than others; and (4) unlike previous findings in the literature, the research questions asked by industry sponsors seem to parallel

those asked by nonindustry sources, and the findings obtained from these trials appear similar in magnitude as those in nonindustry sources.

Based on these findings, statin prescribing patterns over the past decade – and in particular atorvastatin’s exceptional sales performance – are not supported by the current best evidence. Among many significant factors, the lack of comparative effectiveness evidence at the time of market entry may have played an indirect role in determining statin prescribing patterns. To meet the information needs of prescribers, regulators should consider requiring comparative evidence at the time of new drug approval. Regulatory agencies such as the Food and Drug Administration are uniquely positioned to oversee the drug development process and influence the nature of clinical evidence at an early stage. During clinical development, regulators and pharmaceutical companies have an opportunity to collaborate to choose comparators, determine sample sizes of future trials, and identify relative treatment effect modifiers for exploration of heterogeneity. Although requiring active comparator trials remains to be the ultimate goal, it is not conceivable that new drugs will be compared to all existing alternatives in randomized controlled trials – at least in the short term. By allowing for a comparison of all relevant drugs – even when they are not trialed against each other –conducting prospectively designed network meta-analyses would facilitate the “comparative” aspect of an expanded comparative effectiveness research agenda. Network meta-analysis can inform approval decisions, may help decrease the likelihood of inferior treatments being approved, and would help focus downstream comparative effectiveness research efforts by streamlining the information needs of regulators, insurers, prescribers, and patients.

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## **THESIS APPENDIX**

## **APPENDIX 1: Study Protocol**

**COMPARATIVE CLINICAL EFFICACY OF STATINS:  
A SYSTEMATIC REVIEW AND MIXED TREATMENT  
COMPARISON**

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**STUDY PROTOCOL**

FINAL VERSION – 9 December 2010



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## Background

Cardiovascular disease (CVD) is the leading cause of death and a major cause of disability worldwide.<sup>1</sup> In 2003, in the United States alone, CVD accounted for more than 800 thousand deaths. It continues to be a major contributor to health disparities and rising health care costs. In 2006, the economic burden of CVD exceeded \$400 billion.<sup>2</sup>

Blood cholesterol levels are a strong predictor of mortality and morbidity associated with CVD.<sup>3,4</sup> Statins act to lower blood cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis. Currently there are six statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin) marketed in the United States for the almost identical indication of “reducing elevated total-cholesterol, low-density lipoprotein-C, apolipoprotein-B, non-high-density lipoprotein-C, and triglyceride levels and increasing high-density lipoprotein in patients with primary hypercholesterolemia.”<sup>5</sup>

Statins are used for the secondary prevention of cardiovascular events in patients with CVD (including a history of angina or acute myocardial infarction, peripheral arterial disease, or a history of stroke) and for primary prevention in patients who are at increased risk of cardiovascular events because of factors such as smoking, hypertension and diabetes. It is recommended that statins are used in conjunction with lifestyle measures (diet, smoking cessation and exercise) and other appropriate interventions (e.g. adequate control of chronic conditions such as hypertension and diabetes).

Statin therapy, initially focused on patients with established cardiovascular disease, has become widely common as the limits of treatment expanded over time to include persons at progressively lower risk of developing cardiovascular events.<sup>4, 6</sup> As the number of patients in need for statin therapy continues to increase, information regarding the relative clinical value of statins is needed to better inform not only patients and prescribers, but also payers. It is particularly difficult to determine the exact threshold of the level of baseline risk for cardiovascular events at which to start prescription or tailor therapy to patients most likely to benefit from statin treatment.

A large body of literature has demonstrated the clinical efficacy and safety of statins for both primary and secondary prevention of CVD events.<sup>4, 6-12</sup> There are three main limitations of the literature synthesizing the evidence on the efficacy and safety of statin therapy:

- 1. The majority of published meta-analyses include only direct evidence.**

Based on a review of the literature, meta-analyses are largely pair-wise comparisons, often comparing statins to placebo or conventional treatment group. Hence, they are often limited to placebo-controlled studies, with active-comparator trials only assessed in isolation. This focus on

placebo-controlled trials has limitations as there is a large number of active-comparator statin trials, which can contribute to the evidence base. It is therefore important to synthesize the totality of the evidence base on statins.

## **2. The extent to which individual statins differ in terms of efficacy and acceptability is unclear.**

Although prescribers and guideline developers widely believe that similar drugs do not differ in terms of their clinical efficacy, empirical evidence suggests that there may be differences between individual drugs in a class.<sup>13, 14</sup> A number of researchers suggested that assuming that all drugs with a similar mechanism of action are equivalent and can be used interchangeably may be clinically unwarranted.<sup>15-17</sup> With the basic mechanism of cholesterol lowering remaining the same, the six statins differ to a various extent in pharmacological properties and they may differ in terms of their clinical efficacy.<sup>18, 19</sup> As with many drugs in so-called drug classes, the extent to which individual statins vary in terms of efficacy and acceptability is unclear.<sup>20</sup> This is because of the fact that most randomized clinical trials have not tested different statins head-to-head. Additionally, almost all of the meta-analyses ‘lumped’ all statins together as one intervention.<sup>4, 7-11, 21-23</sup>

## **3. Quantitative syntheses of randomized trials have not taken into account the dose-response relationship of statins.**

The majority of published meta-analyses did not explicitly address the potential impact of dose on the clinical efficacy and safety of statins under the assumption that statins at their respective doses have similar clinical efficacy. This assumption cannot be validated and has not been verified in clinical data.

### *Overcoming the limitations of the literature*

**Combination of direct and indirect evidence:** Methodological advances in statistical synthesis approaches, called mixed treatment comparisons (also known as *network meta-analyses*), facilitate the combination of direct and indirect evidence by incorporating both direct (when statins are compared to each other within a trial) and indirect comparisons (when statins are compared between trials with a common comparator treatment, which is often placebo).<sup>24-26</sup>

**Evaluation of the comparative efficacy and acceptability of individual statins:** By implication of including both direct and indirect evidence, attempts at statistically synthesizing the existing body of evidence are no longer limited to a pair-wise comparisons.<sup>27</sup> Rather, they are capable of comparing all relevant statins even when they are not trialed against each other.<sup>28</sup>

Mixed treatment comparisons can summarize randomized trials of individual statins to provide point estimates (together with uncertainty estimates) for their association with a given endpoint,

as well as an estimate of incoherence (that is, a measure of how well the entire network of statins fits together). Mixed treatment comparison methods have been used successfully in other fields of medicine and resulted in influential publications.<sup>29</sup>

**Evaluation of the impact of dose on the comparative efficacy and acceptability of individual statins:** Meta-regression techniques can incorporate the impact of dose on the efficacy and safety of statins.<sup>30, 31</sup> These methods have been developed and implemented in various therapeutic areas.<sup>32</sup>

## Study Objectives

In the current study, the objective is to systematically review the clinical literature to identify and document the comparative clinical efficacy of statins on the basis of both direct and indirect evidence.

Statistical analyses will be conducted to rank the available statins in terms of their efficacy and safety. The objective of the statistical analysis will be to quantitatively compare the clinical efficacy and safety of six statins on the basis of:

1. Surrogate endpoints (for example, reductions in blood cholesterol levels)
2. Clinical events (for example, reductions in the risk of developing CVD events)

## Research Questions

The proposed study will address the following research questions:

1. What is the comparative clinical efficacy and safety of individual statins on the basis of surrogate outcomes independently of the effect on clinical outcomes in primary prevention, secondary prevention, and mixed patient populations?
2. What is the comparative clinical efficacy and safety of individual statins on the basis of clinical outcomes in primary prevention, secondary prevention, and mixed patient populations?

## Methods

### Identification of Studies

The systematic review will be conducted based on the most up-to-date NHS Centre for Dissemination and Review guidelines.<sup>33</sup> Search terms will be pre-defined, and searches will be conducted in MEDLINE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CCTR), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), and Health Technology Assessment Database (NHS

HTA). These electronic databases will be searched starting from January 1, 1985 (approximately five years before the first statin was available on the market).

The search will employ the terms *atorvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, cholesterol, cardiovascular disease, and Hydroxymethylglutaryl-CoA Reductase Inhibitors/therapeutic use*. A manual search will also be performed using the authors' reference files and reference lists from original communications and review articles. Identified qualitative and quantitative systematic reviews (meta-analyses) will be manually reviewed to cross check references and confirm the comprehensiveness of study identification and selection.

Trial databases of regulatory agencies (the Food and Drug Administration (FDA) in the USA, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and the European Medicines Agency (EMA) in the EU) and ongoing trial registers (clinicaltrials.gov in the USA, ISRCTN and National Research Register in the UK) will be hand-searched for published, unpublished and ongoing randomized controlled trials.

#### **Exclusion Criteria**

The following exclusion criteria will be applied to the articles identified in each of the searches:

- Quasi-randomized trials or non-randomized studies
- Studies of multi-interventional therapies where the effect of the statin cannot be separated out
- Case reports, comments, letters, editorials, and review articles
- *In vitro* or animal studies
- Studies in populations other than primary and secondary prevention of CVD
- Studies in pediatric patient populations, less than 18 years old
- Studies with short follow-up duration (<4 weeks)
- Studies with no arms having more than 50 patients
- Studies not reporting detailed dosing regimens received by patients on all comparator arms (that is, it must be clear whether the study employed fixed or variable dosing regimens)

#### **Inclusion Criteria**

The following inclusion criteria will be applied to the articles identified by each of the searches:

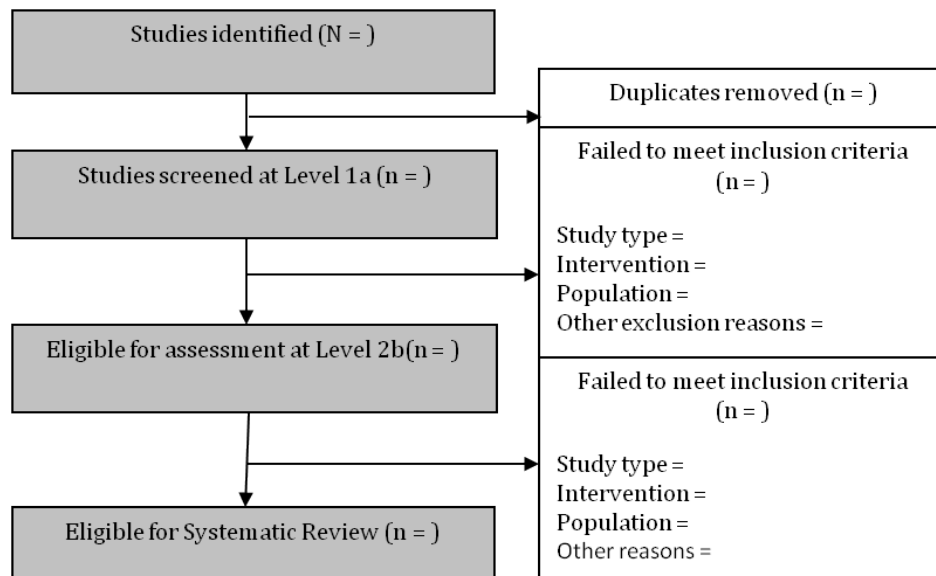
- Randomized controlled studies (randomized, prospective, controlled design); both open-label and double-blind designs will be included

- Patients in at least one arm of the trial must receive atorvastatin, fluvastatin, losuvastatin, pravastatin, rosuvastatin, and simvastatin (either generic or brand-name formulations)
- The patients of interest are patients at least 18 years of age with, or at risk of developing, CVD (primary and secondary prevention populations)
- To be included in the statistical analysis, each selected study must report either surrogate endpoints (e.g. reductions in blood cholesterol levels), or clinical events of interest (e.g. reductions in the risk of developing CVD events). Outcomes of interest are also listed below.

Trials with crossover design will only be included if results are available from the first randomized period. Studies that compared multiple doses of the same statin will be included. Both fixed-dose and titration trials will be included.

Titles and abstracts of studies identified from the searches described above will be screened by one researcher based on the exclusion criteria (Level 1 screening; Figure below). Full texts of studies accepted at Level 1 will be further reviewed by two researchers at Level 2 employing the inclusion criteria (Figure). At Level 2, if there is an uncertainty on the study relevance, the reviewers will resolve the issue by consensus.

The inclusion/exclusion processes will be documented thoroughly, including completion of the PRISMA flow chart as shown below.<sup>34</sup>



A list of included and excluded studies with the reasons for exclusion will be established.

## **Data Extraction**

We will use a structured data-abstraction form implemented in Microsoft Excel to ensure consistency of appraisal for each study.

Data on the following items will be extracted:

### Study-level Characteristics

- Trial (trial reference)
- Population severity (narrative description of CVD risk factors of the patient population)
- Patient population (primary prevention, secondary prevention, or mixed population)
- Dosing regimen (fixed-dose or titration trial)
- Co-morbid conditions (condition of primary interest is diabetes)
- Concomitant medication usage
- Trial duration in weeks
- Follow-up duration in weeks (time point at which outcomes are reported)
- Primary statin and dosage
- Comparator(s) and dosage(s) (these can be other statin treatments, placebo, usual care, or no treatment)
- Number of patients in each study arm (number randomized to each study arm)

### Surrogate and Clinical Endpoints

- Mean reduction in LDL concentration from baseline
- Mean reduction in HDL concentration from baseline
- Mean reduction in total cholesterol from baseline
- Number of CVD deaths (cardiovascular deaths)
- Number of stroke deaths (both hemorrhagic and ischemic stroke)
- Number of all-cause deaths (all-cause mortality)
- Number of CVD events (non-fatal myocardial infarctions, non-fatal stroke)
- Number of MACE events (composite outcome of CVD death, myocardial infarction, and stroke)

Once the list of included studies is finalized, two researchers will extract data independently. Discrepancies will be settled through consensus discussion. In the event of conflict, a third researcher will be recruited, whose decision will be considered final.

#### **Trial categorization and subgroups**

Whenever possible, included trials will be categorized as either primary or secondary prevention trials. Primary prevention trials are those that assessed the efficacy and safety of statins in patients free of CVD at baseline. Secondary prevention trials are those that evaluated statins in patients with established CVD. Given that a number of trials will include both primary and secondary prevention populations, these trials will be categorized as having a mixed patient population. In cases where study authors reported data separately on a sole primary prevention or secondary prevention group within a mixed trial, this information will be recorded for use in respective statistical analysis. To account for the possibility that the efficacy of statins may be different across clinically defined sub-groups, further categorization will be conducted. Whenever available, results will be recorded by age (<65 or >65 years), sex, or diabetes status.

#### **Quality Assessment of Included Trials**

The quality of randomized controlled trials will be assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination.<sup>33</sup> Where inadequate information on trial characteristics are provided, the trial authors will be contacted in order to obtain further information. As with data extraction, potential disagreements will be resolved by consensus.

#### **Statistical Analysis**

All analyses will be performed separately for primary prevention, secondary prevention, and mixed patient populations.

The analysis will be based on the total number of randomly assigned participants, irrespective of how the original study investigators analyzed the data. Therefore, outcome data for the intent-to-treat population will be used. When data on dropouts are carried forward and included in the efficacy evaluation (Last Observation Carried Forward, LOCF), they will be analyzed according to the primary studies.

#### *Synthesis of Results*

Included trials will first be summarized in terms of patient and trial characteristics. Trial and patient population characteristics will be tabulated, describing the types of direct and indirect comparisons and some important variables, both clinical and methodological (such as trial population, year of publication, age, risk of CVD, sponsorship, etc.).

For each pair-wise comparison between statins, the relative effect will be calculated with a 95% CI. First, we will perform classical pair-wise meta-analyses to synthesize studies that compare the same interventions using the Der Simonian Laird method.<sup>35</sup> Forest plots of the relative treatment effects from the individual trials and pair-wise meta-analyses will be visually inspected to search for groups and outliers. This will be statistically supplemented by using the  $I^2$  measure, which will be used to estimate the percentage of total variation among studies that can be considered to be due to heterogeneity.<sup>36</sup> Rough thresholds of 25%, 50%, and 75% will be used to define low, moderate, and high heterogeneity.

To determine the comparative effects of statins, we will conduct mixed treatment comparisons. In these analyses, study-level relative treatment effects will be combined using both fixed- and random-effects models within a Bayesian framework using Markov chain Monte Carlo methods in WinBUGS.<sup>24-27, 37</sup> This will be based on modeling the outcomes in every treatment group of every study, and specifying the relations among the relative effects across studies making different comparisons. The probability that each statin is the most efficacious regimen will be assessed by calculating the treatment effect for each statin compared with the common comparator treatment, and counting the proportion of iterations of the Markov chain in which each drug has the highest treatment effect, the second highest, and so on.

Relevant time points of interest for the mixed treatment analysis will be determined once data extraction is complete. A rate-based model (using hazard rates and their ratios) may be needed to take into account outcomes reported at different follow-up times.

Relative treatment effects will be determined using an “unconstrained” model for the control arm rate of the studies.<sup>25</sup> Thus, the analysis will not allow one study’s placebo rate to give any information about another study’s; there will be no “borrowed strength” across study placebo rates.

Both fixed-effects and random-effects models will be developed for the statistical analysis. The fixed-effects models will be run under the assumption that every trial has an identical underlying A vs. B effect. The random-effects model, which is a more conservative assumption when taking into account potential heterogeneity, will assume that every trial has an identical underlying mean effect, but some degree of variation may be present. The choice of a fixed or random effect meta-analysis model will be made by comparing models regarding their goodness of fit to the data. The goodness of fit will be estimated by calculating the difference between the deviance for the fitted model and the deviance for the saturated model (which fits the data perfectly).

To estimate inconsistency between direct and indirect evidence, we will calculate the ratio of relative effects for indirect versus direct evidence. Inconsistency will be defined as the

disagreement between direct and indirect evidence with a 95% CI excluding 1.<sup>38</sup> More formally, we will adopt the node-split method. In the node-split method, a model that assumes consistency across the entire set of comparisons in the treatment network will be compared with one that relaxes the consistency assumption for the individual comparison (node) being assessed.<sup>39</sup> Using this method, the amount of agreement between the direct and indirect evidence will be formally measured.

A systematic procedure will be followed to ensure that the choice of initial values used in WinBugs models do not have a substantial impact on the findings. The convergence of models in WinBugs will be initially challenged by performing 3-chain analyses with widely dispersed starting values and evaluating their convergence using the Brooks-Gelman-Rubin (BGR) diagnostic plots.

### *Consideration of Dose*

In contrast to the approach adopted by earlier statin meta-analyses, studies that used variable doses (titrating) will not be excluded.<sup>7</sup> Instead, where trials provided data on the proportion of patients at each dose, the number in the treatment arm will be proportioned out to the correct dosage (and hence included in the analysis).<sup>40</sup> Even where trials did not provide data on the proportion of patients at each dose, trials will be categorized as 'titration trials' and included in the analysis.

Four sets of analyses will be conducted to explicitly consider the impact of dose on the comparative treatment effects of statins. The first set of analyses will pool trials with fixed-dose and titration designs to evaluate the comparative efficacy and safety of statins irrespective of dose. Secondary analyses will include only titration trials.

The effect of dose on comparative treatment effects will be an essential consideration in additional statistical analyses. As the literature does not provide a clear answer as to how dose should be taken into account, two types of analyses will be conducted. One set of mixed treatment comparison analyses will be conducted for the dose-specific comparators (e.g. rosuvastatin 10-20mg vs. atorvastatin 10-20mg). Therefore, drug efficacy will be defined as the reduction in cholesterol concentration (or the reduction in CVD event occurrence) for a given dose. This analysis will compare all potential drug-dose combinations (comparing 18 dose-drug combinations to each other: 6 statins, each with low-medium-high dosages). Another set of analyses will be conducted for comparisons at the drug-level (e.g. rosuvastatin vs. atorvastatin) and will compare six statins. The drug-level analysis will use a meta-regression to take into account the dose-response relationship of each individual statin. Recent methodological advances allow meta-regression techniques to be applied to mixed treatment comparisons.<sup>30, 31</sup>

### *Planned sensitivity analyses*

1. Dosing regimen: Based on the understanding that titration trials may provide essential information that better represent actual clinical practice, analyses will test the sensitivity of separating out the comparative effect of statins in titration trials.
2. Baseline risk: We will perform exploratory meta-regressions (using study-level age, LDL, HDL as covariates) to evaluate whether the effects of baseline severity and the size of the relative treatment effect can be separated.
3. Trial duration: It has been suggested that statin therapy does not immediately impact on the number of patients having a CVD event. Therefore, studies shorter than 20 weeks of follow-up will be excluded in analyses of CVD outcomes.
4. Priors: Sensitivity of the findings to prior distributions will be evaluated by varying the prior distributions from less informative to more informative values and examining the variability observed in the credibility intervals of point estimates. One prior will be extremely vague, while the other (to be employed in the base-case analyses) will be vague but slightly informative.
5. Population: Sensitivity of the findings to patient populations (primary prevention, secondary prevention, mixed) will be assessed in comprehensive analyses by first pooling all trials together and then introducing meta-regression coefficients to take into account potential differences across patient populations.
6. Publication year: Sensitivity of the findings to publication year (as a proxy for evolving trial protocols and potentially different patient populations over the years) will be assessed by incorporating publication year as a meta-regression coefficient in the analysis.
7. Blinding in trials: It is possible that the findings obtained in double-blind trials differ than those from open-label trials. To test the sensitivity of the findings to the blinding in trials, separate analyses will be conducted for double-blind and open-label trials.

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## **APPENDIX 2: Example WinBugs Code**

## Generic WinBugs code used in Chapter 4: Dose-Comparative Effects of Individual Statins on Cholesterol Levels

*Normal likelihood, identity link*

Random effects model for multi-arm trials

```
model{
for(i in 1:ns){
  w[i,1] <- 0
  delta[i,1] <- 0
  mu[i] ~ dnorm(0,.0001)
  for (k in 1:na[i]) {
    var[i,k] <- pow(se[i,k],2)
    prec[i,k] <- 1/var[i,k]
    y[i,k] ~ dnorm(theta[i,k],prec[i,k])
    theta[i,k] <- mu[i] + delta[i,k]
    dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
  }
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
    md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
    taud[i,k] <- tau *2*(k-1)/k
    w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)
  }
}
totresdev <- sum(resdev[])
d[1]<-0
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)
tau <- pow(sd,-2)
A ~ dnorm(meanA,precA)
for (k in 1:nt) { T[k] <- A + d[k] }
}
```

**Generic WinBugs code in used in Chapter 5: Comparative Benefits of Individual Statins  
and Chapter 6: Comparative Harms of Individual Statins**

*Binomial likelihood, logit link*

Random effects model for multi-arm trials

```

model{
for(i in 1:ns){
  w[i,1] <- 0
  delta[i,1] <- 0
  mu[i] ~ dnorm(0,.0001)
  for (k in 1:na[i]) {
    r[i,k] ~ dbin(p[i,k],n[i,k])
    logit(p[i,k]) <- mu[i] + delta[i,k]
    rhat[i,k] <- p[i,k] * n[i,k]
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])))
      + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))    }
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
      md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
      taud[i,k] <- tau * 2*(k-1)/k
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
  }
  totesdev <- sum(resdev[])
  d[1]<-0
  for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
  sd ~ dunif(0,5) # vague prior for between-trial SD
  tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
  A ~ dnorm(meanA,precA)
  for (k in 1:nt) { logit(T[k]) <- A + d[k] }
}

```

**Generic WinBugs code used in Chapter 7: Methodological Quality and Risk of Bias in Randomized Controlled Trials of Statins**

Normal likelihood, identity link

Random effects model for multi-arm trials, *fixed effect model for bias*

```

model{
for(i in 1:ns){
  w[i,1] <- 0
  b[i,1] <- 0
  delta[i,1] <- 0
  mu[i] ~ dnorm(0,.0001)
  for (k in 1:na[i]) {
    var[i,k] <- pow(se[i,k],2)
    prec[i,k] <- 1/var[i,k]
    y[i,k] ~ dnorm(theta[i,k],prec[i,k])
    theta[i,k] <- mu[i] + delta[i,k] + beta*b[i,k]
    dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
  }
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
    md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
    taud[i,k] <- tau *2*(k-1)/k
    w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)
  }
}
totresdev <- sum(resdev[])
d[1] <- 0
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,10)
tau <- pow(sd,-2)
beta ~ dnorm(0, .0001)
for (c in 1:(nt-1)) {
  for (k in (c+1):nt) { meandif[c,k] <- (d[k]-d[c]) }
}
}

```

## Generic WinBugs code used in Chapter 7: Methodological Quality and Risk of Bias in Randomized Controlled Trials of Statins

### Normal likelihood, identity link

Random effects model for multi-arm trials, *random effects model for bias*

```
model{
for(i in 1:ns){
  w[i,1] <- 0
  b[i,1] <- 0
  beta[i,1] <- 0
  delta[i,1] <- 0
  mu[i] ~ dnorm(0,.0001)
  for (k in 1:na[i]) {
    var[i,k] <- pow(se[i,k],2)
    prec[i,k] <- 1/var[i,k]
    y[i,k] ~ dnorm(theta[i,k],prec[i,k])
    theta[i,k] <- mu[i] + delta[i,k] + beta[i,k]*b[i,k]
    dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
  }
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {
    beta[i,k] ~ dnorm(B, Pkappa)
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
    md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
    taud[i,k] <- tau *2*(k-1)/k
    w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)
  }
}
totresdev <- sum(resdev[])
d[1] <- 0
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,10)
tau <- pow(sd,-2)

kappa ~ dunif(0,10)
kappa.sq <- pow(kappa,2)
Pkappa <- 1/kappa.sq
B ~ dnorm(0,.0001)
for (c in 1:(nt-1)) {
  for (k in (c+1):nt) { meandif[c,k] <- (d[k]-d[c]) }
}
}
```

### **APPENDIX 3: List of Included Trials**

**Appendix Table 1** – References and characteristics of included trials.

#	Reference	Trial Name	Population Category	Treatment	Dose of Treatment	Number of Randomized Patients	Dosing Regimen
1	(1988). "A multicenter comparison of lovastatin and cholestyramine therapy for severe primary hypercholesterolemia. The Lovastatin Study Group III." JAMA 260(3): 359-66.	LSG-III	Hypercholesterolemia with or without CHD	Lovastatin	40mg/day	87	Fixed
				Lovastatin	80mg/day	89	
2	(1993). "Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. The Pravastatin Multinational Study Group for Cardiac Risk Patients." Am J Cardiol 72(14): 1031-7.	PMSG	Hypercholesterolemia with or without CHD	Pravastatin	20mg/day	530	Fixed
				Control	NA	532	
3	(1993). "Comparison of the efficacy, safety and tolerability of simvastatin and pravastatin for hypercholesterolemia. The Simvastatin Pravastatin Study Group." Am J Cardiol 71(16): 1408-14.	SPSG	Hypercholesterolemia with or without CHD	Simvastatin	Started at 10mg/day	275	Titration*
				Pravastatin	Started at 10mg/day	275	

4	(1993). "A multicenter comparative trial of lovastatin and pravastatin in the treatment of hypercholesterolemia. The Lovastatin Pravastatin Study Group." Am J Cardiol 71(10): 810-5.	LPSG	Hypercholesterolemia with or without CHD	Lovastatin	80mg/day	339	Titration**
				Pravastatin	40mg/day	333	
5	(1994). "Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)." Lancet 344(8934): 1383-9.	4S	Secondary Prevention	Control	NA	2223	Titration
				Simvastatin	Started at 20mg/day	2221	
6	(1994). "Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS)." Lancet 344(8923): 633-8.	MAAS	Secondary Prevention	Control	NA	188	Fixed
				Simvastatin	20mg/day	193	
7	(1997). "The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. The Post Coronary Artery Bypass Graft Trial Investigators." N Engl J Med 336(3): 153-162.	POST-CABG	Secondary Prevention	Lovastatin	Started at 40mg/day	676	Titration
				Lovastatin	Started at 2.5mg/day	675	
8	(1998). "Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group." N Engl J Med 339(19): 1349-57.	LIPID	Secondary Prevention	Control	NA	4502	Fixed
				Pravastatin	40mg/day	4512	

9	(2000). "Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)." Ital Heart J 1(12): 810-820.	GISSI-P	Secondary Prevention	Pravastatin	20mg/day	2138	Fixed
				Control	NA	2133	
10	Albert, M. A., E. Danielson, et al. (2001). "Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study." JAMA 286(1): 64-70.	PRINCE	Primary Prevention	Control	NA	837	Fixed
				Pravastatin	40mg/day	865	
11	Athysros, V. G., A. A. Papageorgiou, et al. (2002) Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Current medical research and opinion Volume, 220-8	GREACE	Secondary Prevention	Atorvastatin	Started at 10mg/day	800	Titration
				Control	NA	800	
12	Bak, A. A., J. Huizer, et al. (1998). "Diet and pravastatin in moderate hypercholesterolaemia: a randomized trial in 215 middle-aged men free from cardiovascular disease." J Intern Med 244(5): 371-8.	Bak et al. 1998	Primary Prevention	Control	NA	54	Fixed
				Pravastatin	20mg/day	53	
13	Barter, P. J. and R. C. O'Brien (2000). "Achievement of target plasma cholesterol levels in	Barter et al. 2000	Hypercholesterolemia with or without CHD	Atorvastatin	Started at 10mg/day	691	Titration*

	hypercholesterolaemic patients being treated in general practice." <i>Atherosclerosis</i> 149(1): 199-205.			Simvastatin	Started at 10mg/day	337	
14	Behounek, B. D., M. E. McGovern, et al. (1994). "A multinational study of the effects of low-dose pravastatin in patients with non-insulin-dependent diabetes mellitus and hypercholesterolemia. Pravastatin Multinational Study Group for Diabetes." <i>Clin Cardiol</i> 17(10): 558-62.	PMSG-Diabetes	Primary Prevention in Diabetes	Pravastatin	Started at 10mg/day	167	Titration
				Control	NA	158	
15	Bertolini, S., G. B. Bon, et al. (1997). "Efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia." <i>Atherosclerosis</i> 130(1-2): 191-7.	Bertolini et al. 1997	Hypercholesterolemia with or without CHD	Atorvastatin	Started at 10mg/day	227	Titration*
				Pravastatin	Started at 20mg/day	78	
16	Bertrand, M. E., E. P. McFadden, et al. (1997). "Effect of pravastatin on angiographic restenosis after coronary balloon angioplasty. The PREDICT Trial Investigators. Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty." <i>J Am Coll Cardiol</i> 30(4): 863-9.	PREDICT	Secondary Prevention	Control	NA	348	Fixed
				Pravastatin	40mg/day	347	
17	Bestehorn, H. P., U. F. Rensing, et al. (1997). "The effect of simvastatin on progression of coronary artery disease. The Multicenter coronary Intervention Study (CIS)." <i>Eur Heart J</i> 18(2): 226-34.	CIS	Secondary Prevention	Simvastatin	Started at 20mg/day	129	Titration
				Control	NA	125	
18	Binbrek, A. S., A. Elis, et al. (2006) Rosuvastatin versus atorvastatin in achieving lipid goals in patients at high risk for cardiovascular disease in clinical practice: A randomized, open-label, parallel-group, multicenter study (DISCOVERY	DISCOVERY-Alpha	Hypercholesterolemia with or without CHD	Rosuvastatin	10mg/day	555	Fixed
				Atorvastatin	10mg/day	382	

	Alpha study). Current Therapeutic Research - Clinical and Experimental Volume, 21-43						
19	Blankenhorn, D. H., S. P. Azen, et al. (1993). "Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS)." Ann Intern Med 119(10): 969-76.	MARS	Secondary Prevention	Lovastatin	Started at 40mg/day	123	Titration
				Control	NA	124	
20	Bradford, R. H., C. L. Shear, et al. (1994). "Expanded Clinical Evaluation of Lovastatin (EXCEL) study results: two-year efficacy and safety follow-up." Am J Cardiol 74(7): 667-73.	EXCEL	Hypercholesterolemia with or without CHD	Control	NA	1663	Titration
				Lovastatin	Started at 20mg/day	6582	
21	Branchi, A., A. M. Fiorenza, et al. (2001). "Effects of low doses of simvastatin and atorvastatin on high-density lipoprotein cholesterol levels in patients with hypercholesterolemia." Clin Ther 23(6): 851-7.	Branchi et al. 2001	Hypercholesterolemia with or without CHD	Atorvastatin	10mg/day	117	Fixed
				Simvastatin	20mg/day	118	
22	Byington, R. P., C. D. Furberg, et al. (1995). "Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II)." Am J Cardiol 76(9): 54C-59C.	PLAC-II	Secondary Prevention	Control	NA	76	Titration
				Pravastatin	Started at 20mg/day	75	
23	Cannon, C. P., E. Braunwald, et al. (2004) Intensive versus moderate lipid lowering with statins after acute coronary syndromes. The New England journal of medicine Volume, 1495-504 DOI:	PROVE IT-TIMI 22	Acute Coronary Syndrome	Pravastatin	Started at 40mg/day	2063	Titration
				Atorvastatin	80mg/day	2099	
24	Colhoun, H. M., D. J. Betteridge, et al. (2004) Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in	CARDS	Primary Prevention in Diabetes	Control	NA	1410	Fixed

	the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet Volume, 685-96			Atorvastatin	10mg/day	1428	
25	Crouse, J. R., J. S. Raichlen, et al. (2007) Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA : the journal of the American Medical Association Volume, 1344-53	METEOR	Primary Prevention	Rosuvastatin	40mg/day	702	Fixed
				Control	NA	282	
26	Davidson, M., J. McKenney, et al. (1997). "Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia. Atorvastatin Study Group I." Am J Cardiol 79(11): 1475-81.	ASG-I	Hypercholesterolemia with or without CHD	Atorvastatin	10mg/day	529	Fixed
				Lovastatin	20mg/day	120	
27	Davidson, M., E.A. Stein, et al. (1997). "The Efficacy and Six-Week Tolerability of Simvastatin 80 and 160mg/day" Am J Cardiol 79(11): 38-42.	Davidson et al. 1997	Hypercholesterolemia with or without CHD	Simvastatin	40mg/day	147	Fixed
				Simvastatin	80mg/day	147	
28	Deedwania, P., P. H. Stone, et al. (2007) Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). Circulation Volume, 700-7	SAGE	Secondary Prevention	Atorvastatin	80mg/day	446	Fixed
				Pravastatin	40mg/day	445	
29	Downs, J. R., M. Clearfield, et al. (1998). "Primary prevention of acute coronary events with lovastatin in men and women with	AFCAPS/TexCAPS	Primary Prevention	Control	NA	3301	Titration

	average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study." JAMA 279(20): 1615-22.			Lovastatin	Started at 20mg/day	3304	
30	Eriksson, M., K. Hadell, et al. (1998). "Compliance with and efficacy of treatment with pravastatin and cholestyramine: a randomized study on lipid-lowering in primary care." J Intern Med 243(5): 373-80.	Eriksson et al. 1998	Primary Prevention	Pravastatin	20mg/day	532	Fixed
				Pravastatin	40mg/day	525	
31	Furberg, C. D., H. P. Adams, Jr., et al. (1994). "Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group." Circulation 90(4): 1679-87.	ACAPS	Primary prevention	Control	NA	459	Titration
				Lovastatin	Started at 20mg/day	460	
32	I, L. Tavazzi, et al. (2008) Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet Volume, 1231-9 DOI:	GISSI-HF	Heart Failure	Rosuvastatin	10mg/day	2285	Fixed
				Control	NA	2289	
33	Glasser, S. P., R. DiBianco, et al. (1996). "The efficacy and safety of pravastatin in patients aged 60 to 85 years with low-density lipoprotein cholesterol > 160 mg/dl." Am J Cardiol 77(1): 83-5.	Glasser et al. 1996	Hypercholesterolemia with or without CHD	Pravastatin	20mg/day	258	Fixed
				Control	NA	89	
34	Hedblad, B., J. Wikstrand, et al. (2001). "Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: Main results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS)." Circulation	BCAPS	Primary Prevention	Control	NA	398	Fixed
				Fluvastatin	40mg/day	395	

	103(13): 1721-1726.						
35	Herd, J. A., C. M. Ballantyne, et al. (1997). "Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS])." Am J Cardiol 80(3): 278-86.	LCAS	Secondary Prevention	Fluvastatin	40mg/day	156	Fixed
				Control	NA	163	
36	Insull, W., S. Kafonek, et al. (2001). "Comparison of efficacy and safety of atorvastatin (10mg) with simvastatin (10mg) at six weeks. ASSET Investigators." Am J Cardiol 87(5): 554-9.	ASSET	Hypercholesterolemia with or without CHD	Atorvastatin	10mg/day	730	Fixed
				Simvastatin	10mg/day	694	
37	Jacobson, T. A., M. M. Chin, et al. (1995). "Efficacy and safety of pravastatin in African Americans with primary hypercholesterolemia." Arch Intern Med 155(17): 1900-6.	Jacobson et al. 1995	Primary Prevention	Pravastatin	20mg/day	182	Fixed
				Control	NA	63	
38	Jukema, J. W., A. V. Bruschke, et al. (1995). "Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS)." Circulation 91(10): 2528-40.	REGRESS	Secondary Prevention	Pravastatin	40mg/day	450	Fixed
				Control	NA	434	
39	Kleemann, A., S. Eckert, et al. (1999). "Effects of lovastatin on progression of non-dilated and dilated coronary segments and on restenosis in patients after PTCA. The cholesterol lowering atherosclerosis PTCA trial	CLAPT	Secondary Prevention	Lovastatin	Started at 20mg/day	112	Titration
				Control	NA	114	

	(CLAPT)." Eur Heart J 20(19): 1393-406.						
40	Kyeong, H. Y., H. Y. Park, et al. (2007) Comparison of efficacy and safety after administering high potency statin to high risk patients: Rosuvastatin 10 mg versus atorvastatin 20 mg. Korean Circulation Journal Volume, 154-60	Kyeong et al. 2007	Acute Coronary Syndrome	Rosuvastatin	10mg/day	60	Fixed
				Atorvastatin	20mg/day	57	
41	Marz, W., H. Wollschlager, et al. (1999). "Safety of low-density lipoprotein cholesterol reduction with atorvastatin versus simvastatin in a coronary heart disease population (the TARGET TANGIBLE trial)." Am J Cardiol 84(1): 7-13.	TARGET TANGIBLE	Secondary Prevention	Atorvastatin	Started at 10mg/day	1897	Titration
				Simvastatin	Started at 10mg/day	959	
42	Mercuri, M., M. G. Bond, et al. (1996). "Pravastatin reduces carotid intima-media thickness progression in an asymptomatic hypercholesterolemic mediterranean population: the Carotid Atherosclerosis Italian Ultrasound Study." Am J Med 101(6): 627-34.	CAIUS	Primary Prevention	Pravastatin	40mg/day	151	Fixed
				Control	NA	154	
43	Milionis, H. J., A. I. Kakafika, et al. (2004) Effects of statin treatment on uric acid homeostasis in patients with primary hyperlipidemia. American heart journal Volume, 635-40	Milionis et al. 2004	Primary Prevention	Atorvastatin	40mg/day	90	Fixed
				Simvastatin	40mg/day	90	
44	Muldoon, M. F., S. D. Barger, et al. (2000). "Effects of lovastatin on cognitive function and psychological well-being." Am J Med 108(7): 538-46.	Muldoon et al. 2000	Primary Prevention	Control	NA	96	Fixed
				Lovastatin	20mg/day	98	

45	Nakamura, Y., O. Yamaoka, et al. (1996). "Pravastatin reduces restenosis after coronary angioplasty of high grade stenotic lesions: results of SHIPS (SHiga Pravastatin Study)." Cardiovasc Drugs Ther 10(4): 475-83.	SHIGA Pravastatin Study	Secondary Prevention	Pravastatin	20mg/day	102	Fixed
				Control	NA	105	
46	Napoli, C., M. Leccese, et al. (1998). "Effects of vitamin E and HMG-CoA reductase inhibition on cholesteryl ester transfer protein and lecithin-cholesterol acyltransferase in hypercholesterolemia." Coron Artery Dis 9(5): 257-64.	Napoli et al. 1998	Primary Prevention	Pravastatin	40mg/day	52	Fixed
				Control	NA	52	
47	Ose, L., M. H. Davidson, et al. (2000). "Lipid-altering efficacy and safety of simvastatin 80 mg/day: long-term experience in a large group of patients with hypercholesterolemia. World Wide Expanded Dose Simvastatin Study Group." Clin Cardiol 23(1): 39-46.	WWEDSS	Hypercholesterolemia with or without CHD	Simvastatin	40mg/day	436	Fixed
				Simvastatin	80mg/day	669	
48	Ostadal, P., D. Alan, et al. (2010) Fluvastatin in the first-line therapy of acute coronary syndrome: results of the multicenter, randomized, double-blind, placebo-controlled trial (the FACS-trial). Trials Volume, 61	FACS	Acute Coronary Syndrome	Fluvastatin	80mg/day	78	Fixed
				Control	NA	78	
49	Pietro, D. A., S. Alexander, et al. (1989). "Effects of simvastatin and probucol in hypercholesterolemia (Simvastatin Multicenter Study Group II)." Am J Cardiol 63(11): 682-6.	Simvastatin Multicenter Study Group II	Hypercholesterolemia with or without CHD	Simvastatin	20mg/day	82	Fixed
				Simvastatin	40mg/day	80	
50	Pitt, B., G. B. Mancini, et al. (1995). "Pravastatin limitation of atherosclerosis in the coronary	PLAC-I	Secondary Prevention	Pravastatin	40mg/day	206	Fixed

	arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation." J Am Coll Cardiol 26(5): 1133-9.			Control	NA	202	
51	Raggi, P, M. Davidson, et al. (2005) Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). Circulation Volume, 563-71	BELLES	Primary Prevention	Atorvastatin	80mg/day	305	Fixed
				Pravastatin	40mg/day	309	
52	Riegger, G., C. Abletshauser, et al. (1999). "The effect of fluvastatin on cardiac events in patients with symptomatic coronary artery disease during one year of treatment." Atherosclerosis 144(1): 263-70.	Riegger et al. 1999	Secondary Prevention	Fluvastatin	Started at 40mg/day	187	Titration
				Control	NA	178	
53	Sacks, F. M., M. A. Pfeffer, et al. (1996). "The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators." N Engl J Med 335(14): 1001-9.	CARE	Secondary Prevention	Control	40mg/day	2078	Fixed
				Pravastatin	NA	2081	
54	Sahni, R., A. R. Maniet, et al. (1991). "Prevention of restenosis by lovastatin after successful coronary angioplasty." Am Heart J 121(6 Pt 1): 1600-1608.	Sahni et al. 1991	Secondary Prevention	Lovastatin	Started at 20mg/day	79	Titration
				Control	NA	78	
55	Salonen, R., K. Nyyssonen, et al. (1995). "Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary	KAPS	Primary Prevention	Control	NA	223	Fixed

	preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries." Circulation 92(7): 1758-1764.			Pravastatin	40mg/day	224	
56	Schwartz, G. G., A. G. Olsson, et al. (2001). "Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial." JAMA 285(13): 1711-8.	MIRACL	Acute Coronary Syndrome	Control	NA	1548	Fixed
				Atorvastatin	80mg/day	1538	
57	Seed, M. and M. R. Weir (1999). "Double-masked comparison of the quality of life of hypercholesterolemic men treated with simvastatin or pravastatin. International Quality of Life Multicenter Group." Clin Ther 21(10): 1758-70.	IQLMG	Hypercholesterolemia with or without CHD	Simvastatin	20mg/day	194	Fixed
				Pravastatin	40mg/day	193	
58	Serruys, P. W., D. P. Foley, et al. (1999). "A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty; final results of the fluvastatin angiographic restenosis (FLARE) trial." Eur Heart J 20(1): 58-69.	FLARE	Secondary Prevention	Fluvastatin	80mg/day	409	Fixed
				Control	NA	425	
59	Shepherd, J., S. M. Cobbe, et al. (1995). "Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group." N Engl J Med 333(20): 1301-7.	WOSCOPS	Primary Prevention	Control	NA	3293	Fixed
				Pravastatin	40mg/day	3302	

60	Smilde, T. J., S. van Wissen, et al. (2001). "Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial." Lancet 357(9256): 577-81.	ASAP	Familial hypercholesterolemia with or without CHD	Atorvastatin	Started at 40mg/day	162	Titration**
				Simvastatin	Started at 20mg/day	168	
61	Stein, E., R. Kreisberg, et al. (1990). "Effects of simvastatin and cholestyramine in familial and nonfamilial hypercholesterolemia. Multicenter Group I." Arch Intern Med 150(2): 341-5.	Stein et al. 1990	Hypercholesterolemia with or without CHD	Simvastatin	20mg/day	84	Fixed
				Simvastatin	40mg/day	81	
62	Stein, E. A., M. H. Davidson, et al. (1998). "Efficacy and safety of simvastatin 80 mg/day in hypercholesterolemic patients. The Expanded Dose Simvastatin U.S. Study Group." Am J Cardiol 82(3): 311-6.	EDS-US	Primary Prevention	Simvastatin	40mg/day	207	Fixed
				Simvastatin	80mg/day	314	
63	Teo, K. K., J. R. Burton, et al. (2000). "Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT)." Circulation 102(15): 1748-1754.	SCAT	Secondary Prevention	Simvastatin	Started at 10mg/day	230	Titration
				Control	NA	230	
64	Waters, D., L. Higginson, et al. (1994). "Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial." Circulation 89(3): 959-68.	CCAIT	Secondary Prevention	Lovastatin	Started at 20mg/day	165	Titration
				Control	NA	166	

65	Weintraub, W. S., S. J. Boccuzzi, et al. (1994). "Lack of effect of lovastatin on restenosis after coronary angioplasty. Lovastatin Restenosis Trial Study Group." N Engl J Med 331(20): 1331-7.	LRTSG	Secondary Prevention	Lovastatin	80mg/day	203	Fixed
				Control	NA	201	
66	Weir, M. R., M. L. Berger, et al. (1996). "Comparison of the effects on quality of life and of the efficacy and tolerability of lovastatin versus pravastatin. The Quality of Life Multicenter Group." Am J Cardiol 77(7): 475-9.	QLMG	Primary Prevention	Lovastatin	40mg/day	211	Fixed
				Pravastatin	40mg/day	215	
67	(2002). "Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)." JAMA 288(23): 2998-3007.	ALLHAT-LTT	Primary Prevention	Pravastatin	Started at 20mg/day	5170	Titration
				Control	NA	5185	
68	(2002). "MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial." Lancet 360(9326): 7-22.	MRC/BHF Heart Protection Study	Hypercholesterolemia with or without CHD	Simvastatin	40mg/day	10269	Fixed
				Control	NA	10267	
69	Ballantyne, C. M., M. A. Blazing, et al. (2003). "Effect on high-density lipoprotein cholesterol of maximum dose simvastatin and atorvastatin in patients with hypercholesterolemia: results of the Comparative HDL Efficacy and Safety Study (CHESS)." Am Heart J 146(5): 862-869.	CHESS	Hypercholesterolemia with or without CHD	Simvastatin	80mg/day	453	Fixed
				Atorvastatin	80mg/day	464	

70	Ballantyne, C. M., J. Hour, et al. (2003). "Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial." <i>Circulation</i> 107(19): 2409-2415.	Ballantyne et al. 2003	Hypercholesterolemia with or without CHD	Atorvastatin	Started at 10mg/day	248	Titration
				Control	NA	60	
71	Bays, H. E., C. A. Dujovne, et al. (2003). "Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADVICOR Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE])." <i>Am J Cardiol</i> 91(6): 667-672.	ADVOCATE	Hypercholesterolemia with or without CHD	Atorvastatin	Started at 10mg/day	82	Titration*
				Simvastatin	Started at 10mg/day	76	
72	Bruckert, E., M. Lievre, et al. (2003). "Short-term efficacy and safety of extended-release fluvastatin in a large cohort of elderly patients." <i>Am J Geriatr Cardiol</i> 12(4): 225-231.	Bruckert et al. 2003	Primary Hypercholesterolemia	Fluvastatin	80mg/day	607	Fixed
				Control	NA	622	
73	Davidson, M. H., T. McGarry, et al. (2002). "Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia." <i>J Am Coll Cardiol</i> 40(12): 2125-34.	Davidson et al. 2002-b	Hypercholesterolemia with or without CHD	Control	NA	70	Fixed
				Simvastatin	Started at 10mg/day	263	
74	Kent, S. M., P. J. Flaherty, et al. (2003). "Effect of atorvastatin and pravastatin on serum C-reactive protein." <i>Am Heart J</i> 145(2): e8.	Kent et al. 2003	Hypercholesterolemia with or without CHD	Pravastatin	40mg/day	67	Fixed
				Atorvastatin	80mg/day	63	
75	Kerzner, B., J. Corbelli, et al. (2003). "Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia." <i>Am J Cardiol</i> 91(4): 418-424.	Kerzner et al. 2003	Primary Prevention	Lovastatin	Started at 10mg/day	220	Titration
				Control	NA	64	

76	Liem, A. H., A. J. van Boven, et al. (2002). "Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial." Eur Heart J 23(24): 1931-1937.	FLORIDA	Acute Coronary Syndrome	Fluvastatin	80mg/day	265	Fixed
				Control	NA	275	
77	Melani, L., R. Mills, et al. (2003). "Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial." Eur Heart J 24(8): 717-728.	Melani et al. 2003	Primary Hypercholesterolemia	Pravastatin	Started at 10mg/day	205	Titration
				Control	NA	65	
78	Olsson, A. G., M. Eriksson, et al. (2003). "A 52-week, multicenter, randomized, parallel-group, double-blind, double-dummy study to assess the efficacy of atorvastatin and simvastatin in reaching low-density lipoprotein cholesterol and triglyceride targets: the treat-to-target (3T) study." Clin Ther 25(1): 119-138.	TREAT TO TARGET	Secondary Prevention	Atorvastatin	20mg/day	552	Titration*
				Simvastatin	20mg/day	535	
79	Sawayama, Y., C. Shimizu, et al. (2002). "Effects of probucol and pravastatin on common carotid atherosclerosis in patients with asymptomatic hypercholesterolemia. Fukuoka Atherosclerosis Trial (FAST)." J Am Coll Cardiol 39(4): 610-616.	FAST	Primary Prevention	Pravastatin	10mg/day	83	Fixed
				Control	NA	81	
80	Serruys, P. W., P. de Feyter, et al. (2002). "Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial." JAMA 287(24): 3215-3222.	LIPS	Secondary Prevention	Fluvastatin	80mg/day	844	Fixed
				Control	NA	833	

81	Shepherd, J., G. J. Blauw, et al. (2002). "Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial." Lancet 360(9346): 1623-1630.	PROSPER	Hypercholesterolemia with or without CHD	Control	NA	1913	Fixed
				Pravastatin	40mg/day	2891	
82	Stein, E. A., K. Strutt, et al. (2003). "Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia." Am J Cardiol 92(11): 1287-1293.	HeFH	Familial hypercholesterolemia with or without CHD	Rosuvastatin	Started at 20mg/day	436	Titration
				Atorvastatin	Started at 20mg/day	187	
83	Taylor, A. J., S. M. Kent, et al. (2002). "ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness." Circulation 106(16): 2055-2060.	ARBITER	Hypercholesterolemia with or without CHD	Pravastatin	40mg/day	82	Fixed
				Atorvastatin	80mg/day	79	
84	Zou, Y., D. Hu, et al. (2003). "Lipid-lowering efficacy and safety of varying doses of Simvastatin in patients with early stage acute coronary syndromes: one-year follow-up study." Chin Med J (Engl) 116(6): 853-856.	Zou et al. 2003	Acute Coronary Syndrome	Simvastatin	10mg/day	98	Fixed
				Simvastatin	20mg/day	99	
85	Chan, K. L., K. Teo, et al. (2007). "Rationale, design, and baseline characteristics of a randomized trial to assess the effect of cholesterol lowering on the progression of aortic stenosis: the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) trial." Am Heart J 153(6): 925-931.	ASTRONOMER	Carotid stenosis	Rosuvastatin	40mg/day	134	Fixed
				Control	NA	135	

86	Colivicchi, F., M. Tubaro, et al. (2010). "Full-dose atorvastatin versus conventional medical therapy after non-ST-elevation acute myocardial infarction in patients with advanced non-revascularisable coronary artery disease." Curr Med Res Opin 26(6): 1277-1284.	Colivicchi et al. 2010	Secondary Prevention	Atorvastatin	Started at 20mg/day	146	Titration
				Atorvastatin	80 mg/day	144	
87	Faergeman, O., L. Hill, et al. (2008). "Efficacy and tolerability of rosuvastatin and atorvastatin when force-titrated in patients with primary hypercholesterolemia: results from the ECLIPSE study." Cardiology 111(4): 219-228.	ECLIPSE	Secondary Prevention	Rosuvastatin	Started at 10mg/day	522	Titration*
				Atorvastatin	Started at 10mg/day	514	
88	Hall, A. S., B. M. Jackson, et al. (2009). "A randomized, controlled trial of simvastatin versus rosuvastatin in patients with acute myocardial infarction: the Secondary Prevention of Acute Coronary Events--Reduction of Cholesterol to Key European Targets Trial." Eur J Cardiovasc Prev Rehabil 16(6): 712-721.	SPACE ROCKET	Acute Coronary Syndrome	Rosuvastatin	40mg/day	633	Fixed
				Simvastatin	40mg/day	630	
89	Hong, M. K., D. W. Park, et al. (2009). "Effects of statin treatments on coronary plaques assessed by volumetric virtual histology intravascular ultrasound analysis." JACC Cardiovasc Interv 2(7): 679-688.	Hong et al. 2009	Hypercholesterolemia with or without CHD	Simvastatin	20mg/day	50	Fixed
				Rosuvastatin	10mg/day	50	

90	Kadoglou, N. P., N. Sailer, et al. (2010). "Aggressive lipid-lowering is more effective than moderate lipid-lowering treatment in carotid plaque stabilization." J Vasc Surg 51(1): 114-121.	Kadoglou et al. 2010	Carotid stenosis	Atorvastatin	10-20 mg/d	70	Fixed
				Atorvastatin	80 mg/d	70	
91	Kjekshus, J., E. Apetrei, et al. (2007). "Rosuvastatin in older patients with systolic heart failure." N Engl J Med 357(22): 2248-2261.	CORONA	Heart Failure	Control	NA	2497	Fixed
				Rosuvastatin	10mg/day	2514	
92	Konduracka, E., D. Galicka-Latala, et al. (2008). "Effect of atorvastatin on endothelial function and inflammation in long-duration type 1 diabetic patients without coronary heart disease and arterial hypertension." Diabetes Obes Metab 10(9): 719-725.	Konduracka et al. 2008	Primary Prevention in Diabetes	Atorvastatin	40mg/day	154	Fixed
				Control	NA	50	
93	Kostapanos, M. S., H. J. Milionis, et al. (2008). "Baseline triglyceride levels and insulin sensitivity are major determinants of the increase of LDL particle size and buoyancy induced by rosuvastatin treatment in patients with primary hyperlipidemia." Eur J Pharmacol 590(1-3): 327-332.	Kostapanos et al. 2008	Primary hypercholesterolemia without CHD	Rosuvastatin	20mg/day	60	Fixed
				Control	NA	60	
94	Kurabayashi, M. and T. Yamazaki (2008). "Superior benefit of aggressive lipid-lowering therapy for high- risk patients using statins: the SUBARU study--more	SUBARU	Primary Prevention	Atorvastatin	10mg/day	213	Fixed

	hypercholesterolemic patients achieve Japan Atherosclerosis Society LDL-C goals with rosuvastatin therapy than with atorvastatin therapy." J Atheroscler Thromb 15(6): 314-323.			Rosuvastatin	5mg/day	214	
95	Lablanche, J. M., A. Leone, et al. (2010). "Comparison of the efficacy of rosuvastatin versus atorvastatin in reducing apolipoprotein B/apolipoprotein A-1 ratio in patients with acute coronary syndrome: results of the CENTAURUS study." Arch Cardiovasc Dis 103(3): 160-169.	CENTAURUS	Acute Coronary Syndrome	Rosuvastatin	20 mg/d	437	Fixed
				Atorvastatin	80 mg/d	450	
96	Laks, T., E. Keba, et al. (2008). "Achieving lipid goals with rosuvastatin compared with simvastatin in high risk patients in real clinical practice: a randomized, open-label, parallel-group, multi-center study: the DISCOVERY-Beta study." Vasc Health Risk Manag 4(6): 1407-1416.	DISCOVERY-Beta	Primary hypercholesterolemia with or without CHD	Rosuvastatin	10mg/day	334	Fixed
				Simvastatin	20mg/day	170	
97	Lewis, J. H., M. E. Mortensen, et al. (2007). "Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial." Hepatology 46(5): 1453-1463.	Lewis et al. 2007	Hypercholesterolemia with Chronic, Well Compensated Liver Disease	Pravastatin	80mg/day	163	Fixed
				Control	NA	163	
98	Mok, V. C., W. W. Lam, et al. (2009). "Statins for asymptomatic middle cerebral artery stenosis: The Regression of Cerebral Artery Stenosis study." Cerebrovasc Dis 28(1): 18-25.	RCASS	Cerebral Artery Stenosis	Control	NA	114	Fixed
				Simvastatin	20mg/day	113	

99	Ose, L., D. Budinski, et al. (2009). "Comparison of pitavastatin with simvastatin in primary hypercholesterolaemia or combined dyslipidaemia." <i>Curr Med Res Opin</i> 25(11): 2755-2764.	Ose et al. 2009	Primary hypercholesterolemia	Simvastatin	20mg/day	108	Fixed
				Simvastatin	40mg/day	111	
100	Alcala, A., S. Jansen, et al. (2010). "Statins improve visual field alterations related to hypercholesterolemia." <i>Atherosclerosis</i> 209(2): 510-514.	Alcala et al. 2010	Primary Prevention	Control	NA	70	Fixed
				Pravastatin	40mg/day	61	
101	Amarenco, P., J. Bogousslavsky, et al. (2006). "High-dose atorvastatin after stroke or transient ischemic attack." <i>N Engl J Med</i> 355(6): 549-559.	SPARCL	Secondary Prevention	Atorvastatin	80mg/day	2365	Fixed
				Control	NA	2366	
102	Bae, J. H., E. Bassenge, et al. (2004). "Effects of low-dose atorvastatin on vascular responses in patients undergoing percutaneous coronary intervention with stenting." <i>J Cardiovasc Pharmacol Ther</i> 9(3): 185-192.	Bae et al. 2004	Secondary Prevention	Atorvastatin	10mg/day	105	Fixed
				Control	NA	100	
103	Bays, H. E., L. Ose, et al. (2004). "A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia." <i>Clin Ther</i> 26(11): 1758-1773.	Bays et al. 2004	Primary hypercholesterolemia	Simvastatin	Started at 10mg/day	622	Titration
				Control	NA	148	
104	Betteridge, D. J. and J. M. Gibson (2007). "Effects of rosuvastatin on lipids, lipoproteins and	ANDROMEDA	Primary Prevention in Diabetes	Rosuvastatin	Started at 10mg/day	248	Titration*

	apolipoproteins in the dyslipidaemia of diabetes." Diabet Med 24(5): 541-549.			Atorvastatin	Started at 10mg/day	246	
105	Bonnet, J., R. McPherson, et al. (2008). "Comparative effects of 10-mg versus 80-mg Atorvastatin on high-sensitivity C-reactive protein in patients with stable coronary artery disease: results of the CAP (Comparative Atorvastatin Pleiotropic effects) study." Clin Ther 30(12): 2298-2313.	CAP	Secondary Prevention	Atorvastatin	10mg/day	170	Fixed
				Atorvastatin	80mg/day	170	
106	A to Z de Lemos, J. A., M. A. Blazing, et al. (2004). "Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial." JAMA 292(11): 1307-1316.	A to Z	Acute Coronary Syndrome	Simvastatin	20mg/day	2232	Titration*
				Simvastatin	80mg/day	2265	
107	Asselbergs, F. W., G. F. Diercks, et al. (2004). "Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria." Circulation 110(18): 2809-2816.	PREVEND IT	Microalbuminuria	Control	NA	431	Fixed
				Pravastatin	40mg/day	433	
108	Durazzo, A. E., F. S. Machado, et al. (2004). "Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial." J Vasc Surg 39(5): 967-975	Durazzo et al. 2004	Vascular surgery with or without CHD	Atorvastatin	20mg/day	50	Fixed
				Control	NA	50	
109	Fonseca, F. A., A. Ruiz, et al. (2005). "The DISCOVERY PENTA study: a Direct Statin COmparison of LDL-C	DISCOVERY-Penta	Hypercholesterolemia with or without CHD	Rosuvastatin	10mg/day	358	Fixed

	Value--an Evaluation of Rosuvastatin therapY compared with atorvastatin." Curr Med Res Opin 21(8): 1307-1315.			Atorvastatin	10mg/day	383	
110	Goldberg, A. C., A. Sapre, et al. (2004). "Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial." Mayo Clin Proc 79(5): 620-629.	Goldberg et al. 2004	Primary hypercholesterolemia	Control	NA	93	Titration
				Simvastatin	Started at 10mg/day	349	
111	Harris, J. L., J. R. Hibbeln, et al. (2004). "Statin treatment alters serum n-3 and n-6 fatty acids in hypercholesterolemic patients." Prostaglandins Leukot Essent Fatty Acids 71(4): 263-269.	Harris et al. 2004	Primary Prevention	Control	NA	56	Fixed
				Simvastatin	40mg/day	50	
112	Jukema, J. W., A. H. Liem, et al. (2005). "LDL-C/HDL-C ratio in subjects with cardiovascular disease and a low HDL-C: results of the RADAR (Rosuvastatin and Atorvastatin in different Dosages And Reverse cholesterol transport) study." Curr Med Res Opin 21(11): 1865-1874.	RADAR	Secondary Prevention	Rosuvastatin	Started at 10mg/day	230	Titration*
				Atorvastatin	Started at 20mg/day	231	
113	Knopp, R. H., M. d'Emden, et al. (2006). "Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN)." Diabetes Care 29(7): 1478-1485.	ASPEN - Primary Prevention	Primary Prevention	Atorvastatin	10mg/day	959	Fixed
				Control	NA	946	

114	Knopp, R. H., M. d'Emden, et al. (2006). "Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN)." Diabetes Care 29(7): 1478-1485.	ASPEN -Secondary Prevention	Secondary Prevention	Atorvastatin	10mg/day	252	Fixed
				Control	NA	253	
115	Koren, M. J. and D. B. Hunninghake (2004). "Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the alliance study." J Am Coll Cardiol 44(9): 1772-1779.	ALLIANCE	Secondary Prevention	Atorvastatin	Started at 10mg/day	1217	Titration
				Control	NA	1225	
116	LaRosa, J. C., S. M. Grundy, et al. (2005). "Intensive lipid lowering with atorvastatin in patients with stable coronary disease." N Engl J Med 352(14): 1425-1435.	TNT	Secondary Prevention	Atorvastatin	10mg/day	5006	Fixed
				Atorvastatin	80mg/day	4995	
117	Leiter, L. A., R. S. Rosenson, et al. (2007). "Efficacy and safety of rosuvastatin 40 mg versus atorvastatin 80 mg in high-risk patients with hypercholesterolemia: results of the POLARIS study." Atherosclerosis 194(2): e154-164.	POLARIS	Secondary Prevention	Rosuvastatin	Started at 20mg/day	432	Titration
				Atorvastatin	Started at 40mg/day	439	
118	Makuuchi, H., A. Furuse, et al. (2005). "Effect of pravastatin on progression of coronary atherosclerosis in patients after coronary artery bypass surgery." Circ J 69(6): 636-643.	PCABG	Secondary Prevention	Pravastatin	Started at 10mg/day	152	Titration
				Control	NA	151	

119	Milionis, H. J., E. Rizos, et al. (2006). "Treating to target patients with primary hyperlipidaemia: comparison of the effects of ATOrvastatin and ROSuvastatin (the ATOROS study)." Curr Med Res Opin 22(6): 1123-1131.	ATOROS	Primary Prevention	Rosuvastatin	Started at 10mg/day	60	Titration
				Atorvastatin	Started at 20mg/day	60	
120	Mizuno, K., H. Nakamura, et al. (2004). "A randomized, open-label, comparative study of simvastatin plus diet versus diet alone on angiographic retardation of coronary atherosclerosis in adult Japanese patients: Japanese utilization of simvastatin therapy (JUST) study." Clin Ther 26(6): 878-888.	JUST	Secondary Prevention	Simvastatin	10mg/day	146	Fixed
				Control	NA	153	
121	Mulder, D. J., P. L. van Haelst, et al. (2007). "The effect of aggressive versus conventional lipid-lowering therapy on markers of inflammatory and oxidative stress." Cardiovasc Drugs Ther 21(2): 91-97.	STAT	Secondary Prevention	Simvastatin	40mg/day	119	Fixed
				Atorvastatin	80mg/day	116	
122	Nakagawa, T., T. Kobayashi, et al. (2004). "Randomized, controlled trial of secondary prevention of coronary sclerosis in normocholesterolemic patients using pravastatin: final 5-year angiographic follow-up of the Prevention of Coronary Sclerosis (PCS) study." Int J Cardiol 97(1): 107-114.	PCS	Secondary Prevention	Pravastatin	10mg/day	54	Fixed
				Control	NA	66	
123	Nakamura, H., K. Arakawa, et al. (2006). "Primary prevention of cardiovascular disease with	MEGA	Primary Prevention	Control	NA	3966	Titration

	pravastatin in Japan (MEGA Study): a prospective randomised controlled trial." Lancet 368(9542): 1155-1163.			Pravastatin	Started at 10mg/day	3866	
124	Nissen, S. E., E. M. Tuzcu, et al. (2004). "Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial." JAMA 291(9): 1071-1080.	REVERSAL	Secondary Prevention	Pravastatin	40mg/day	249	Fixed
				Atorvastatin	80mg/day	253	
125	Pedersen, T. R., O. Faergeman, et al. (2005). "High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial." JAMA 294(19): 2437-2445.	IDEAL	Secondary Prevention	Simvastatin	Started at 20mg/day	4449	Titration
				Atorvastatin	Started at 80mg/day	4439	
126	Sardo, M. A., S. Campo, et al. (2005). "Antioxidant effect of atorvastatin is independent of PON1 gene T(-107)C, Q192R and L55M polymorphisms in hypercholesterolaemic patients." Curr Med Res Opin 21(5): 777-784.	Sardo et al. 2005	Primary Prevention	Control	NA	106	Fixed
				Atorvastatin	10mg/day	99	
127	Schmermund, A., S. Achenbach, et al. (2006). "Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial." Circulation 113(3): 427-437.	Schermund et al. 2006	Primary Prevention	Atorvastatin	10mg/day	236	Fixed
				Atorvastatin	80mg/day	235	

128	Sever, P. S., B. Dahlof, et al. (2004). "Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial." Lancet 64 Suppl 2: 43-60.	ASCOT-LLA	Primary Prevention	Atorvastatin	10mg/day	5168	Fixed
				Control	NA	5137	
129	Sola, S., M. Q. Mir, et al. (2006). "Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure." J Am Coll Cardiol 47(2): 332-337.	Sola et al. 2006	Heart Failure	Control	NA	54	Fixed
				Atorvastatin	20mg/day	54	
130	Stone, P. H., D. M. Lloyd-Jones, et al. (2005). "Effect of intensive lipid lowering, with or without antioxidant vitamins, compared with moderate lipid lowering on myocardial ischemia in patients with stable coronary artery disease: the Vascular Basis for the Treatment of Myocardial Ischemia Study." Circulation 111(14): 1747-1755.	Stone et al. 2005	Secondary Prevention	Atorvastatin	80mg/day	96	Titration
				Control	NA	103	
131	Strandberg, T. E., J. Feely, et al. (2004). "Twelve-week, multicenter, randomized, open-label comparison of the effects of rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: a DISCOVERY study." Clin Ther 26(11): 1821-1833.	DISCOVERY	Primary hypercholesterolemia	Rosuvastatin	10mg/day	686	Fixed
				Atorvastatin	10mg/day	338	
132	Wolffenbittel, B. H., A. A. Franken, et al. (2005). "Cholesterol-lowering effects of rosuvastatin compared	CORALL	Primary Prevention in Diabetes	Rosuvastatin	Started at 10mg/day	131	Titration*

	with atorvastatin in patients with type 2 diabetes -- CORALL study." J Intern Med 257(6): 531-539.			Atorvastatin	Started at 20mg/day	132	
133	Yokoi, H., M. Nobuyoshi, et al. (2005). "Three-year follow-up results of angiographic intervention trial using an HMG-CoA reductase inhibitor to evaluate retardation of obstructive multiple atheroma (ATHEROMA) study." Circ J 69(8): 875-883.	ARTHEROMA	Secondary Prevention	Control	NA	146	Titration
				Pravastatin	Started at 10mg/day	142	
134	Yu, C. M., Q. Zhang, et al. (2007). "Comparison of intensive and low-dose atorvastatin therapy in the reduction of carotid intimal-medial thickness in patients with coronary heart disease." Heart 93(8): 933-939.	Yu et al. 2007	Secondary Prevention	Atorvastatin	10mg/day	55	Fixed
				Atorvastatin	80mg/day	57	
135	Park, J. S., Y. J. Kim, et al. (2010). "Comparative study of low doses of rosuvastatin and atorvastatin on lipid and glycemic control in patients with metabolic syndrome and hypercholesterolemia." Korean J Intern Med 25(1): 27-35.	Park et al. 2010	Metabolic Syndrome	Rosuvastatin	10mg/day	172	Fixed
				Atorvastatin	10mg/day	178	
136	Ridker, P. M., E. Danielson, et al. (2008). "Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein." N Engl J Med 359(21): 2195-207.	JUPITER	Primary Prevention	Rosuvastatin	20mg/day	8901	Fixed
				Control	NA	8901	
137	Sato, H., K. Kinjo, et al. (2008). "Effect of early use of low-dose pravastatin on major adverse cardiac events in patients with acute myocardial infarction: the OACIS-LIPID Study." Circ J 72(1): 17-22.	OACIS-LIPID	Acute Coronary Syndrome	Pravastatin	10mg/day	176	Fixed
				Control	NA	177	

138	Sdringola, S., K. L. Gould, et al. (2008). "A 6 month randomized, double blind, placebo controlled, multi-center trial of high dose atorvastatin on myocardial perfusion abnormalities by positron emission tomography in coronary artery disease." Am Heart J 155(2): 245-53.	Sdringola et al. 2008	Secondary Prevention	Control	NA	73	Fixed
				Atorvastatin	80mg/day	72	
139	Zhao, Z., J. Geng, et al. (2009). "Efficacy and safety of atorvastatin during early hospitalization in elderly patients with unstable angina." Clin Exp Pharmacol Physiol 36(5-6): 554-8.	Zhao et al. 2009	Secondary Prevention	Atorvastatin	80mg/day	85	Fixed
				Atorvastatin	20mg/day	79	
140	Zhu, J. R., B. Tomlinson, et al. (2007). "A randomised study comparing the efficacy and safety of rosuvastatin with atorvastatin for achieving lipid goals in clinical practice in Asian patients at high risk of cardiovascular disease (DISCOVERY-Asia study)." Curr Med Res Opin 23(12): 3055-68.	DISCOVERY-Asia	Secondary Prevention	Rosuvastatin	10mg/day	950	Titration
				Atorvastatin	10mg/day	472	
141	Guillen MA, Kornhauser C, Samaniego V, de Tejada AL, Sanchez H. Once-daily pravastatin compared with dietary advice in patients with borderline and moderate primary hypercholesterolemia. Curr Ther Res 1995;56:305-17.	Guillen et al. 1995	Hypercholesterolemia with or without CHD	Control	NA	74	Titration*
				Pravastatin	Started at 10mg/day	76	
142	Clearfield MB, Amerena J, Bassand JP, Hernández García HR, Miller SS, Sosef FF, Palmer MK, Bryzinski BS. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia--Prospective	PULSAR	Secondary Prevention	Rosuvastatin	10mg/day	504	Fixed
				Atorvastatin	20mg/day	492	

	study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR). Trials. 2006 Dec 21;7:35.						
143	Anderssen, S. A., A. K. Hjelstuen, et al. (2005). "Fluvastatin and lifestyle modification for reduction of carotid intima-media thickness and left ventricular mass progression in drug-treated hypertensives." Atherosclerosis 178(2): 387-397.	HYRIM	Primary Prevention	Fluvastatin	40mg/day	142	Fixed
				Control	NA	143	
144	Vrtovec, B., R. Okrajsek, et al. (2008). "Atorvastatin therapy may reduce the incidence of sudden cardiac death in patients with advanced chronic heart failure." J Card Fail 14(2): 140-4.	Vrtovec et al. 2008	Heart Failure	Atorvastatin	10mg/day	55	Fixed
				Control	NA	55	
145	Thompson, P. L., I. Meredith, et al. (2004) Effect of pravastatin compared with placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: the Pravastatin in Acute Coronary Treatment (PACT) trial. American heart journal Volume, e2 DOI:	PACT	Acute Coronary Syndrome	Pravastatin	Started at 20mg/day	1710	Titration
				Control	NA	1698	
146	Berne C, Siewert-Delle A; URANUS study investigators. Comparison of rosuvastatin and atorvastatin for lipid lowering in patients with type 2 diabetes mellitus: results from the URANUS study. Cardiovasc Diabetol. 2005 Jun 3;4:7.	URANUS	Primary Prevention in Diabetes	Rosuvastatin	Started at 10mg/day	232	Titration
				Atorvastatin	Started at 10mg/day	233	
147	(1993). "Comparative efficacy and safety of pravastatin and cholestyramine alone and combined in patients with	PMSGII	Hypercholesterolemia with or without CHD	Control	NA	60	Fixed
				Pravastatin	40mg/day	63	

	hypercholesterolemia. Pravastatin Multicenter Study Group II." Arch Intern Med 153(11): 1321-9.			Pravastatin	80mg/day	63	
148	(2001). "The effect of aggressive versus standard lipid lowering by atorvastatin on diabetic dyslipidemia: the DALI study: a double-blind, randomized, placebo-controlled trial in patients with type 2 diabetes and diabetic dyslipidemia." Diabetes Care 24(8): 1335-41.	DALI	Primary Prevention in Diabetes	Control	NA	72	Fixed
				Atorvastatin	10mg/day	73	
				Atorvastatin	80mg/day	72	
149	Dallongeville, J., J. C. Fruchart, et al. (1994). "Fluvastatin reduces levels of plasma apo B-containing particles and increases those of LpA-I. European Fluvastatin Study Group." Am J Med 96(6A): 32S-36S.	European Fluvastatin Study	Hypercholesterolemia with or without CHD	Control	NA	136	Fixed
				Fluvastatin	20mg/day	117	
				Fluvastatin	40mg/day	170	
150	Farnier, M., J. J. Portal, et al. (2000). "Efficacy of atorvastatin compared with simvastatin in patients with hypercholesterolemia." J Cardiovasc Pharmacol Ther 5(1): 27-32.	Farnier et al. 2000	Hypercholesterolemia with or without CHD	Atorvastatin	10mg/day	109	Fixed
				Simvastatin	20mg/day	109	
				Simvastatin	10mg/day	54	
151	Insull, W., Jr., D. Black, et al. (1994). "Efficacy and safety of once-daily vs twice-daily dosing with fluvastatin, a synthetic reductase inhibitor, in primary hypercholesterolemia." Arch Intern Med 154(21): 2449-55.	Insull et al. 1994	Hypercholesterolemia with or without CHD	Fluvastatin	10mg/day	69	Fixed
				Fluvastatin	20mg/day	70	
				Control	NA	68	
152	Haffner, S., T. Orchard, et al. (1995). "Effect of simvastatin on Lp(a) concentrations." Clin Cardiol 18(5): 261-7.	Haffner et al. 1995	Hypercholesterolemia with or without CHD	Control	NA	86	Fixed
				Simvastatin	10mg/day	88	
				Simvastatin	20mg/day	83	
153	Keech, A., R. Collins, et al. (1994). "Three-year follow-up of the Oxford Cholesterol Study: assessment of	OCS	Secondary Prevention	Simvastatin	40mg/day	206	Fixed
				Simvastatin	20mg/day	208	

	the efficacy and safety of simvastatin in preparation for a large mortality study." Eur Heart J 15(2): 255-69.			Control	NA	207	
154	LaRosa, J. C., W. Applegate, et al. (1994). "Cholesterol lowering in the elderly. Results of the Cholesterol Reduction in Seniors Program (CRISP) pilot study." Arch Intern Med 154(5): 529-39.	CRISP	Hypercholesterolemia with or without CHD	Control	NA	142	Fixed
				Lovastatin	20mg/day	144	
				Lovastatin	40mg/day	145	
155	Paolisso, G., M. Barbagallo, et al. (2000). "Effects of simvastatin and atorvastatin administration on insulin resistance and respiratory quotient in aged dyslipidemic non-insulin dependent diabetic patients." Atherosclerosis 150(1): 121-7.	Paolisso et al 2000	Primary Prevention in Diabetes	Control	NA	67	Fixed
				Simvastatin	10mg/day	61	
				Atorvastatin	5mg/day	67	
156	Stein, E., D. Plotkin, et al. (2000). "Effects of simvastatin (40 and 80 mg/day) in patients with mixed hyperlipidemia." Am J Cardiol 86(4): 406-11.	Stein et al. 2000	Mixed Hyperlipidemia and Diabetes with or without CHD	Control	NA	130	Fixed
				Simvastatin	40mg/day	130	
				Simvastatin	80mg/day	130	
157	Voora, D., S. H. Shah, et al. (2008) Pharmacogenetic predictors of statin-mediated low-density lipoprotein cholesterol reduction and dose response. Circulation. Cardiovascular genetics Volume, 100-6	Voora et al. 2008	Primary Prevention	Atorvastatin	Started at 10mg/day	168	Titration*
				Simvastatin	Started at 20mg/day	182	
				Pravastatin	Started at 10mg/day	159	
158	Mohler, E. R., 3rd, W. R. Hiatt, et al. (2003). "Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease." Circulation 108(12): 1481-1486.	Mohler et al. 2003	Peripheral Arterial Disease	Atorvastatin	10mg/day	120	Fixed
				Atorvastatin	80mg/day	120	
				Control	NA	114	
159	Olsson, A. G., H. Istad, et al. (2002). "Effects of rosuvastatin and	Olsson et al. 2002	Hypercholesterolemia with or without CHD	Rosuvastatin	Started at 5mg/day	138	Titration*

	atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia." Am Heart J 144(6): 1044-1051.			Rosuvastatin	Started at 10mg/day	134	
				Atorvastatin	Started at 10mg/day	140	
160	Kostapanos, M. S., H. J. Milionis, et al. (2009). "Dose-dependent effect of rosuvastatin treatment on HDL-subfraction phenotype in patients with primary hyperlipidemia." J Cardiovasc Pharmacol Ther 14(1): 5-13.	Kostapanos et al. 2009	Primary hypercholesterolemia without CHD	Rosuvastatin	10mg/day	50	Fixed
				Rosuvastatin	20mg/day	50	
				Control	NA	50	
161	Insull, W., Jr., J. K. Ghali, et al. (2007). "Achieving low-density lipoprotein cholesterol goals in high-risk patients in managed care: comparison of rosuvastatin, atorvastatin, and simvastatin in the SOLAR trial." Mayo Clin Proc 82(5): 543-550.	SOLAR	Hypercholesterolemia with or without CHD	Rosuvastatin	10mg/day	542	Titration*
				Atorvastatin	10mg/day	544	
				Simvastatin	20mg/day	546	
162	Schwartz, G. G., M. A. Bolognese, et al. (2004). "Efficacy and safety of rosuvastatin and atorvastatin in patients with hypercholesterolemia and a high risk of coronary heart disease: a randomized, controlled trial." Am Heart J 148(1): e4.	Schwartz et al. 2004	Secondary Prevention	Rosuvastatin	Started at 5mg/day	127	Titration*
				Rosuvastatin	Started at 10mg/day	128	
				Atorvastatin	Started at 10mg/day	128	
163	Stalenhoef, A. F., C. M. Ballantyne, et al. (2005). "A comparative study with rosuvastatin in subjects with metabolic syndrome: results of the COMETS study." Eur Heart J 26(24): 2664-2672.	COMETS	Metabolic Syndrome	Rosuvastatin	10mg/day	165	Titration*
				Atorvastatin	10mg/day	157	
				Control	NA	79	
164	Robinson, J. G., C. M. Ballantyne, et al. (2009). "Lipid-altering efficacy and safety of ezetimibe/simvastatin versus atorvastatin in patients with hypercholesterolemia and the metabolic syndrome (from the	VYMET	Metabolic Syndrome	Atorvastatin	10mg/day	229	Fixed
				Atorvastatin	20mg/day	229	
				Atorvastatin	40mg/day	228	

	VYMET study)." Am J Cardiol 103(12): 1694-702.						
165	Rosenson, R. S., J. D. Otvos, et al. (2009). "Effects of rosuvastatin and atorvastatin on LDL and HDL particle concentrations in patients with metabolic syndrome: a randomized, double-blind, controlled study." Diabetes Care 32(6): 1087-91.	Rosenson et al. 2009	Metabolic Syndrome	Rosuvastatin	10mg/day	136	Fixed
				Atorvastatin	10mg/day	119	
				Control	NA	63	
166	Bots, A. F., J. J. Kastelein, et al. (2005) Achieving lipid goals in real life: the Dutch DISCOVERY study. International journal of clinical practice Volume, 1387-94	DISCOVERY Netherlands	Hypercholesterolemia with or without CHD	Rosuvastatin	10mg/day	621	Fixed
				Atorvastatin	10mg/day	189	
				Simvastatin	20mg/day	194	
				Pravastatin	40mg/day	211	
167	Brown, A. S., R. G. Bakker-Arkema, et al. (1998). "Treating patients with documented atherosclerosis to National Cholesterol Education Program-recommended low-density-lipoprotein cholesterol goals with atorvastatin, fluvastatin, lovastatin and simvastatin." J Am Coll Cardiol 32(3): 665-72.	Brown et al. 1998	Secondary Prevention	Atorvastatin	Started at 10mg/day	78	Titration*
				Fluvastatin	Started at 20mg/day	76	
				Lovastatin	Started at 20mg/day	78	
				Simvastatin	Started at 10mg/day	76	
168	Crouse, J. R., 3rd, J. Frohlich, et al. (1999). "Effects of high doses of simvastatin and atorvastatin on high-density lipoprotein cholesterol and apolipoprotein A-I." Am J Cardiol 83(10): 1476-1477, A1477.	Crouse et al. 1999	Hypercholesterolemia with or without CHD	Simvastatin	40mg/day	202	Fixed
				Atorvastatin	20mg/day	210	
				Simvastatin	80mg/day	215	
				Atorvastatin	40mg/day	215	
169	Hunninghake, D. B., R. H. Knopp, et al. (1990). "Efficacy and safety of pravastatin in patients with primary hypercholesterolemia. I. A dose-response study."	Hunninghake et al. 1990	Hypercholesterolemia with or without CHD	Control	NA	88	Fixed
				Pravastatin	10mg/day	65	
				Pravastatin	20mg/day	56	

	Atherosclerosis 85(1): 81-9.			Pravastatin	40mg/day	59	
170	Jacotot, B., J. D. Banga, et al. (1994). "Efficacy of a low dose-range of fluvastatin (XU 62-320) in the treatment of primary hypercholesterolaemia. A dose-response study in 431 patients. The French-Dutch Fluvastatin Study Group." Br J Clin Pharmacol 38(3): 257-63.	FDFS	Hypercholesterolemia with or without CHD	Control	NA	86	Fixed
				Fluvastatin	5mg/day	85	
				Fluvastatin	10mg/day	85	
				Fluvastatin	20mg/day	87	
171	Recto, C. S., 2nd, S. Acosta, et al. (2000). "Comparison of the efficacy and tolerability of simvastatin and atorvastatin in the treatment of hypercholesterolemia." Clin Cardiol 23(9): 682-8.	Recto et al. 2000	Hypercholesterolemia with or without CHD	Simvastatin	20mg/day	125	Fixed
				Simvastatin	40mg/day	126	
				Atorvastatin	10mg/day	125	
				Atorvastatin	20mg/day	126	
172	Brown, W. V., H. E. Bays, et al. (2002). "Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial." Am Heart J 144(6): 1036-1043.	Brown et al. 2002	Hypercholesterolemia with or without CHD	Rosuvastatin	Started on 5mg/day	123	Titration*
				Rosuvastatin	Started on 10mg/day	116	
				Pravastatin	Started on 20mg/day	118	
				Simvastatin	Started on 20mg/day	120	
173	Davidson, M., P. Ma, et al. (2002). "Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia." Am J Cardiol 89(3): 268-275.	Davidson et al. 2002	Hypercholesterolemia with or without CHD	Control	NA	132	Fixed
				Rosuvastatin	5mg/day	129	
				Rosuvastatin	10mg/day	130	
				Atorvastatin	10mg/day	128	
174	Karalis, D. G., A. M. Ross, et al.	CHALLENGE	Hypercholesterolemia	Atorvastatin	10mg/day	639	Fixed

	(2002). "Comparison of efficacy and safety of atorvastatin and simvastatin in patients with dyslipidemia with and without coronary heart disease." Am J Cardiol 89(6): 667-671.		with or without CHD	Atorvastatin	80mg/day	207	
				Simvastatin	20mg/day	641	
				Simvastatin	80mg/day	207	
175	Paoletti, R., M. Fahmy, et al. (2001). "Rosuvastatin demonstrates greater reduction of low-density lipoprotein cholesterol compared with pravastatin and simvastatin in hypercholesterolaemic patients: a randomized, double-blind study." J Cardiovasc Risk 8(6): 383-390.	Paoletti et al. 2001	Hypercholesterolemia with or without CHD	Rosuvastatin	5mg/day	119	Fixed
				Rosuvastatin	10mg/day	111	
				Pravastatin	20mg/day	136	
				Simvastatin	20mg/day	129	
176	IRIS Deedwania, P. C., M. Gupta, et al. (2007). "Comparison of rosuvastatin versus atorvastatin in South-Asian patients at risk of coronary heart disease (from the IRIS Trial)." Am J Cardiol 99(11): 1538-1543.	IRIS	Hypercholesterolemia with or without CHD	Rosuvastatin	10mg/day	189	Fixed
				Rosuvastatin	20mg/day	182	
				Atorvastatin	10mg/day	185	
				Atorvastatin	20mg/day	184	
177	Ferdinand, K. C., L. T. Clark, et al. (2006). "Comparison of efficacy and safety of rosuvastatin versus atorvastatin in African-American patients in a six-week trial." Am J Cardiol 97(2): 229-235.	ARIES	Familial hypercholesterolemia and combined hyperlipoproteinemia	Rosuvastatin	10mg/day	195	Fixed
				Rosuvastatin	20mg/day	196	
				Atorvastatin	10mg/day	191	
				Atorvastatin	20mg/day	192	
178	Lloret, R., J. Ycas, et al. (2006). "Comparison of rosuvastatin versus atorvastatin in Hispanic-Americans with hypercholesterolemia (from the STARSHIP trial)." Am J Cardiol 98(6): 768-773.	STARSHIP	Hypercholesterolemia with or without CHD	Rosuvastatin	10mg/day	184	Fixed
				Rosuvastatin	20mg/day	173	
				Atorvastatin	10mg/day	168	
				Atorvastatin	20mg/day	171	
179	Andrews, T. C., C. M. Ballantyne, et al. (2001). "Achieving and maintaining National Cholesterol Education Program low-density	Ballantyne et al. 2001	Hypercholesterolemia with or without CHD	Atorvastatin	Started at 10mg/day	1902	Titration*
				Fluvastatin	Started at 20mg/day	477	

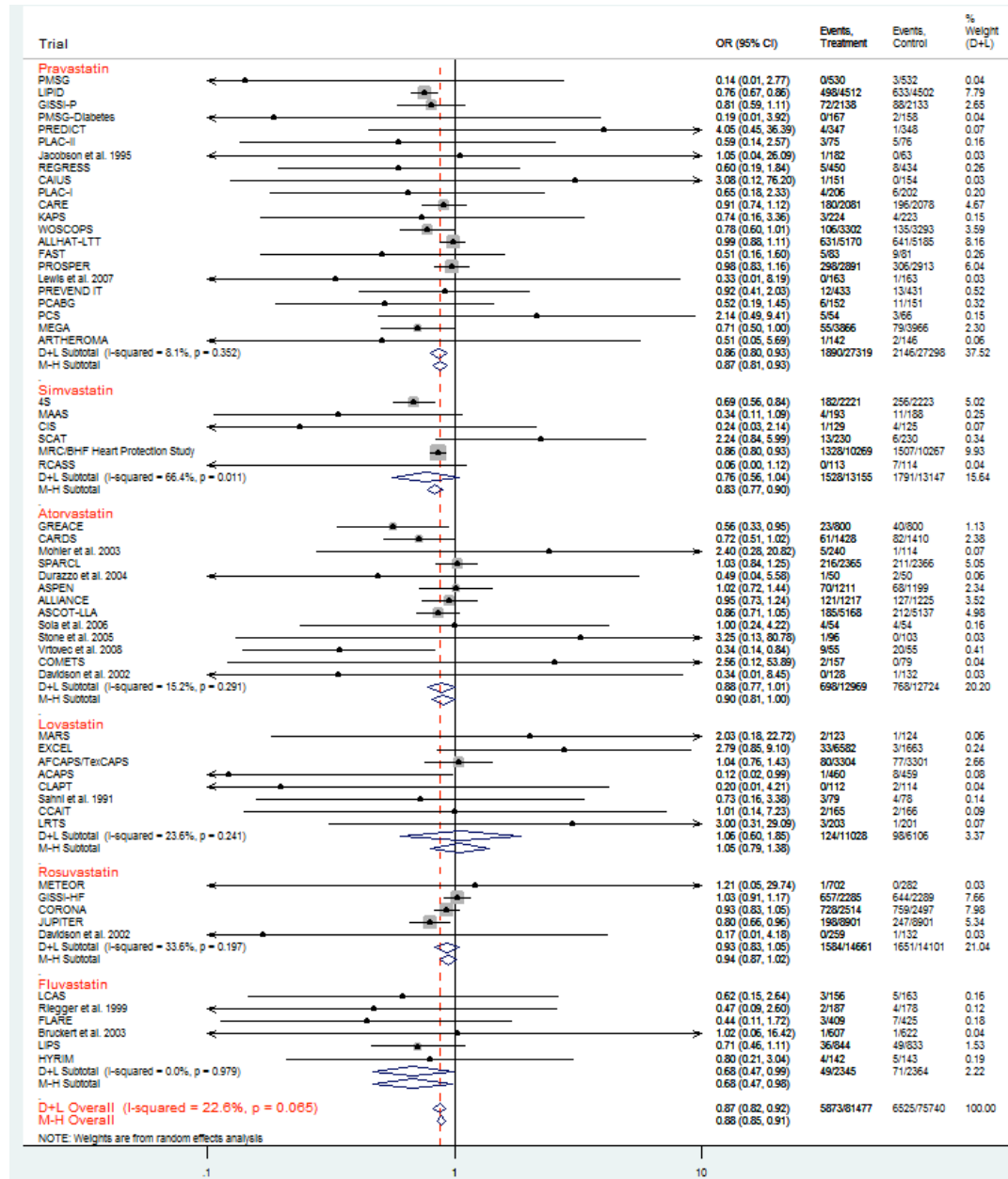
	lipoprotein cholesterol goals with five statins." Am J Med 111(3): 185-91.			Lovastatin	Started at 20mg/day	476	
				Pravastatin	Started at 10mg/day	462	
				Simvastatin	Started at 10mg/day	468	
180	Gentile, S., S. Turco, et al. (2000). "Comparative efficacy study of atorvastatin vs simvastatin, pravastatin, lovastatin and placebo in type 2 diabetic patients with hypercholesterolaemia." Diabetes Obes Metab 2(6): 355-62.	Gentile et al. 2000	Primary Prevention in Diabetes	Atorvastatin	10mg/day	84	Fixed
				Simvastatin	10mg/day	78	
				Pravastatin	20mg/day	81	
				Lovastatin	20mg/day	80	
				Control	NA	86	
181	Davidson, M. H., J. Palmisano, et al. (2003). "A multicenter, randomized, double-blind clinical trial comparing the low-density lipoprotein cholesterol-lowering ability of lovastatin 10, 20, and 40 mg/d with fluvastatin 20 and 40 mg/d." Clin Ther 25(11): 2738-2753.	Davidson et al. 2003	Primary Hypercholesterolemia	Lovastatin	10mg/day	167	Fixed
				Lovastatin	20mg/day	164	
				Lovastatin	40mg/day	170	
				Fluvastatin	20mg/day	170	
				Fluvastatin	40mg/day	167	
182	Ballantyne, C. M., M. Bertolami, et al. (2006). "Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapy (MERCURY) II." Am Heart J 151(5): 975 e971-979.	MERCURY II	Hypercholesterolemia with or without CHD	Rosuvastatin	20mg/day	392	Fixed
				Atorvastatin	10mg/day	403	
				Atorvastatin	20mg/day	395	
				Simvastatin	20mg/day	402	
				Simvastatin	40mg/day	401	
183	Cheung, R. C., J. M. Morrell, et al. (2005). "Effects of switching statins on lipid and apolipoprotein ratios in the MERCURY I study." Int J Cardiol 100(2): 309-316.	MERCURY I	Hypercholesterolemia with or without CHD	Rosuvastatin	10mg/day	538	Fixed
				Atorvastatin	10mg/day	529	
				Atorvastatin	20mg/day	925	

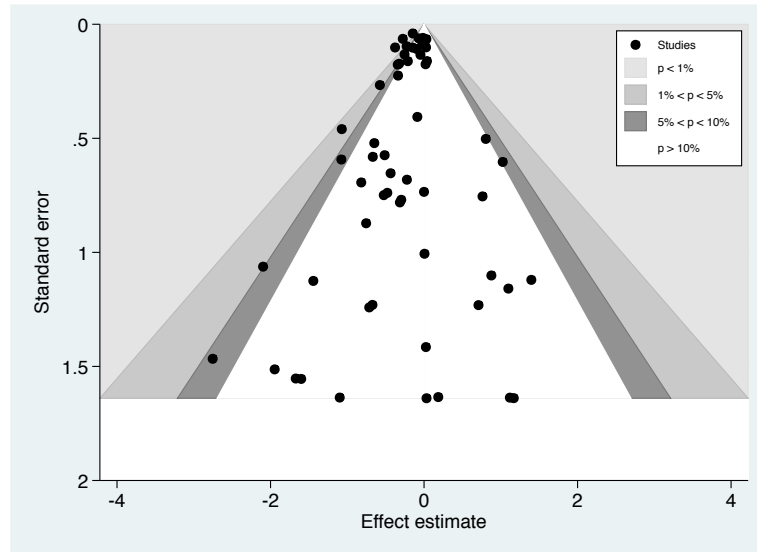
				Simvastatin	20mg/day	543	
				Pravastatin	40mg/day	521	
184	Jones, P. H., M. H. Davidson, et al. (2003). "Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial)." Am J Cardiol 92(2): 152-160.	STELLAR	Primary Prevention	Rosuvastatin	10mg/day	158	Fixed
				Rosuvastatin	20mg/day	164	
				Rosuvastatin	40mg/day	158	
				Atorvastatin	10mg/day	158	
				Atorvastatin	20mg/day	156	
				Atorvastatin	40mg/day	160	
				Atorvastatin	80mg/day	167	
				Simvastatin	10mg/day	167	
				Simvastatin	20mg/day	164	
				Simvastatin	40mg/day	159	
				Simvastatin	80mg/day	165	
				Pravastatin	10mg/day	162	
				Pravastatin	20mg/day	166	
				Pravastatin	40mg/day	164	

## **APPENDIX 4: Findings of Pair-wise Meta-analyses and Evaluation of Small Study Effects**

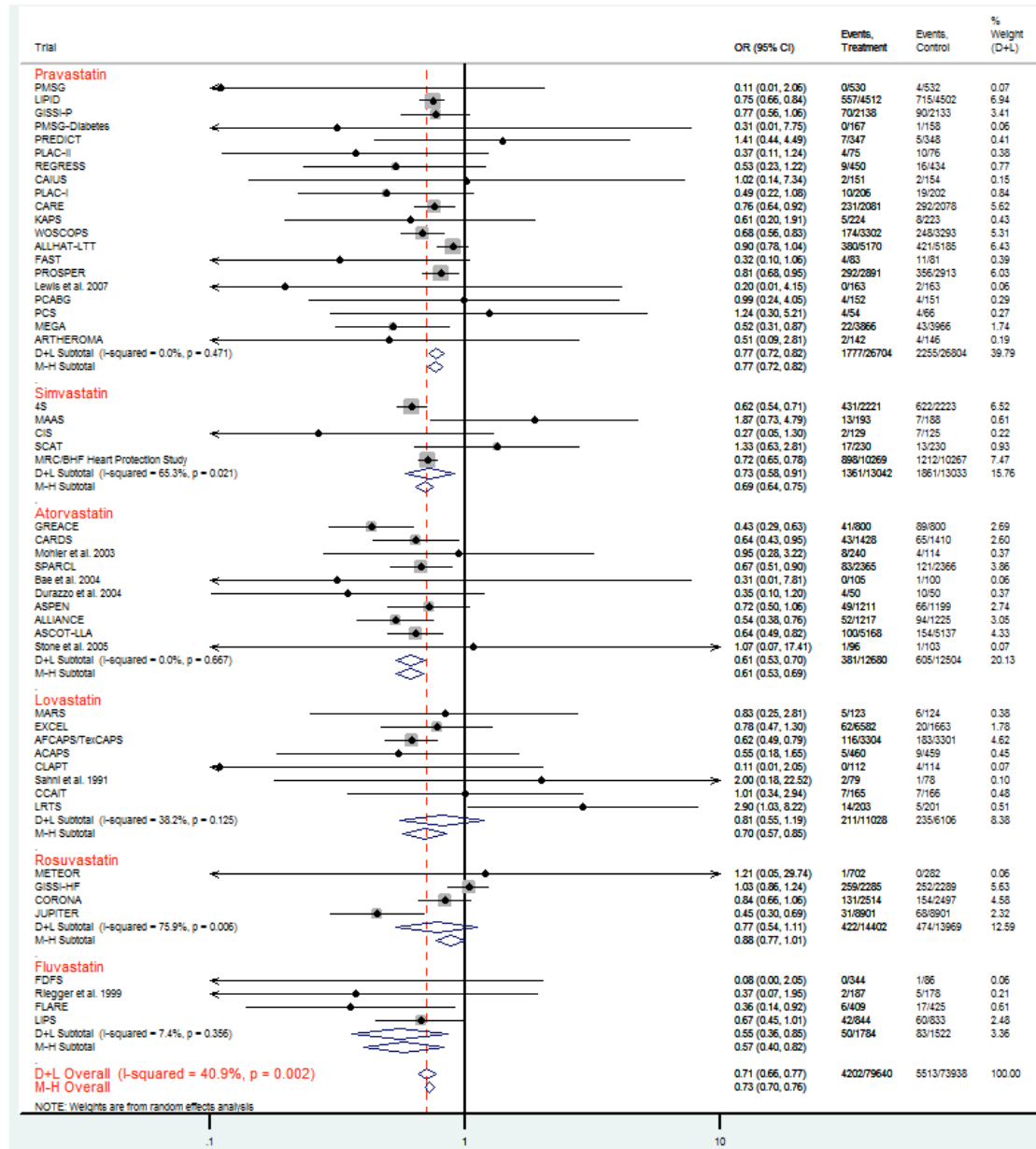
**Appendix Figure 1** – Effect of statins compared to control in placebo-controlled randomized trials of participants with and without prior coronary heart disease at baseline (overall population) for (A) all-cause mortality; (B) major coronary events; (C) major cerebrovascular events; (D) discontinuations due to adverse events, (E) myalgia, (F) transaminase elevations, and (G) creatine kinase elevations. Also shown are contour-enhanced funnel plots for the assessment of small study effects.

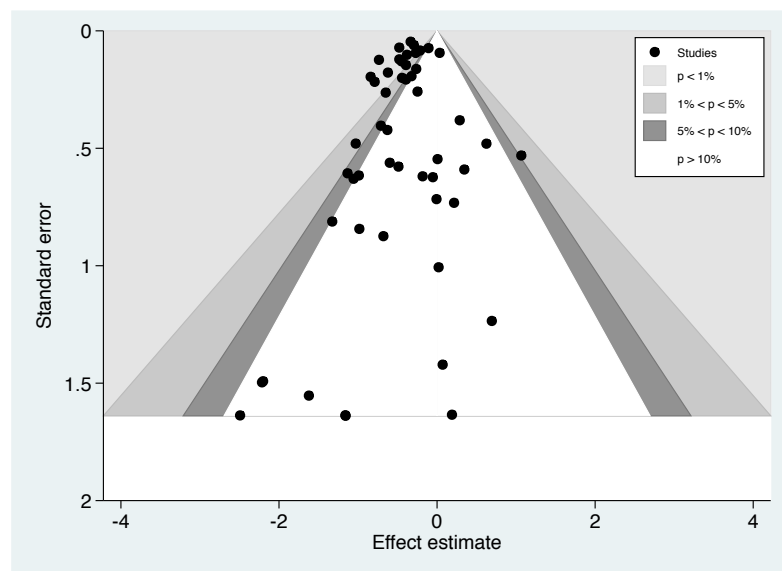
**(A) All-cause mortality**



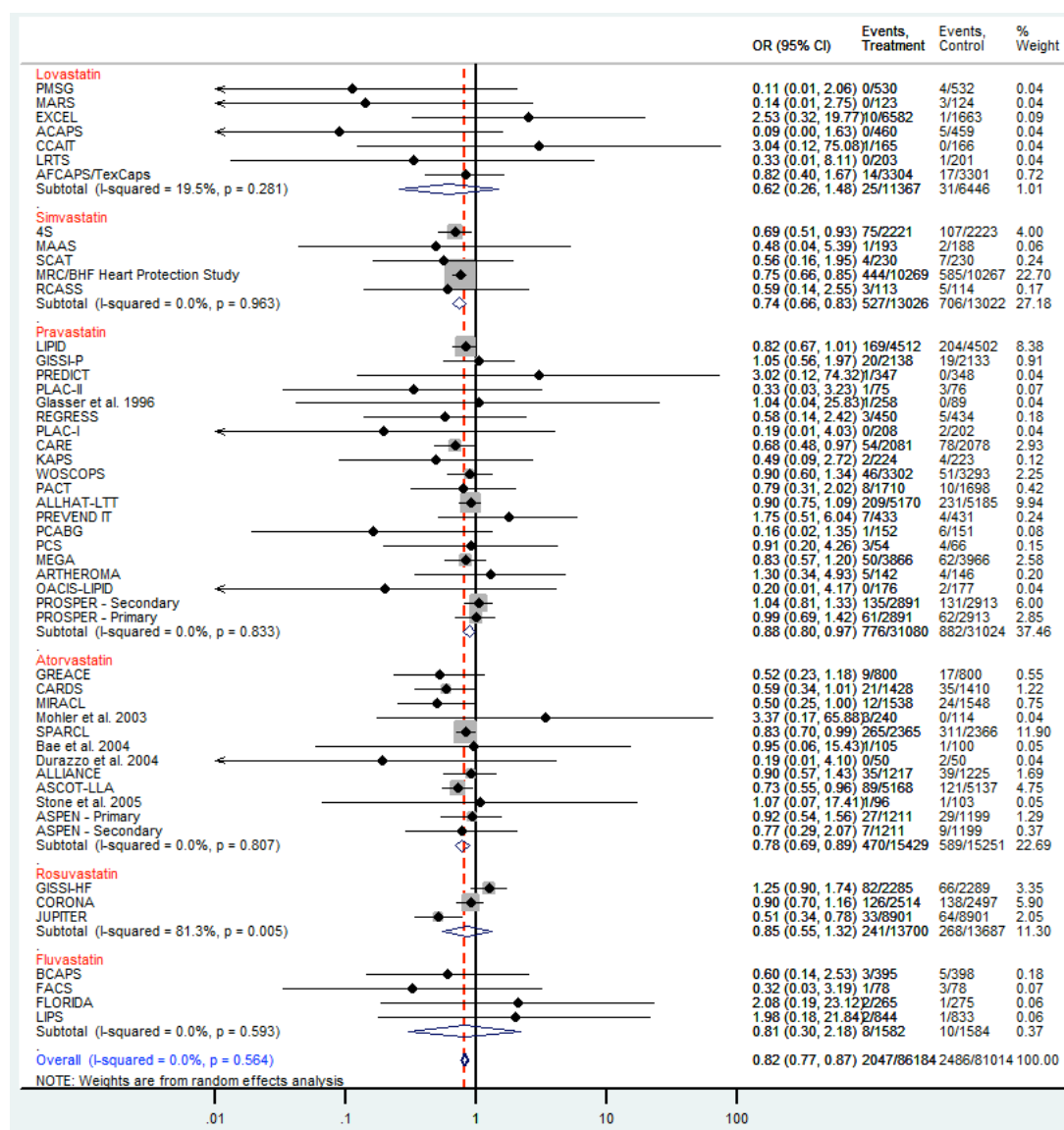


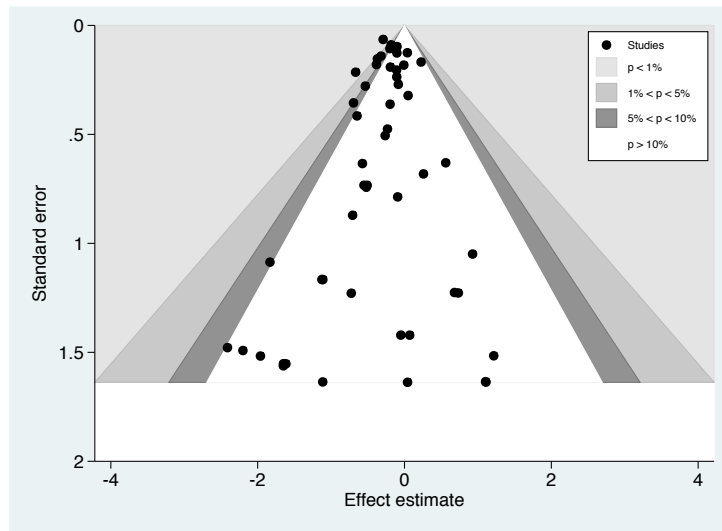
## (B) Major coronary events



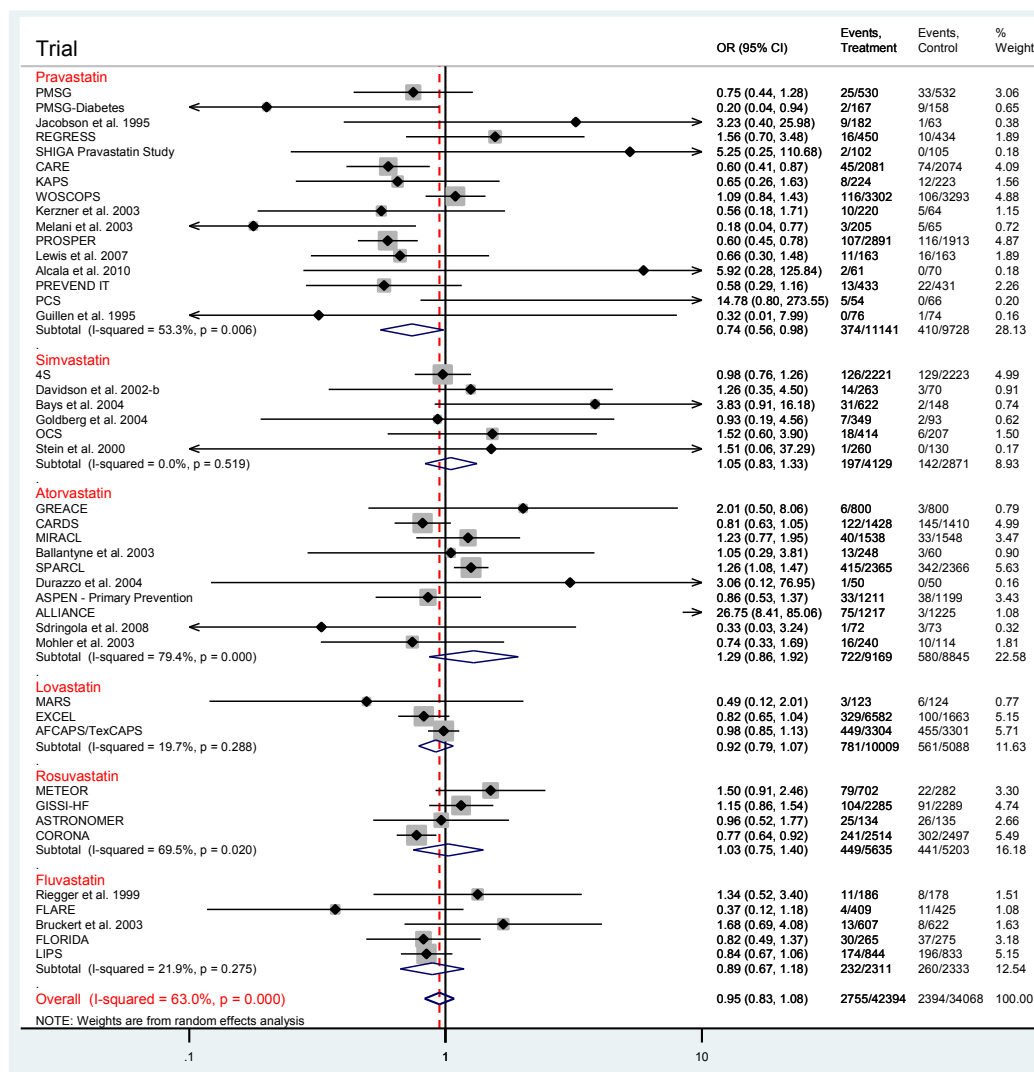


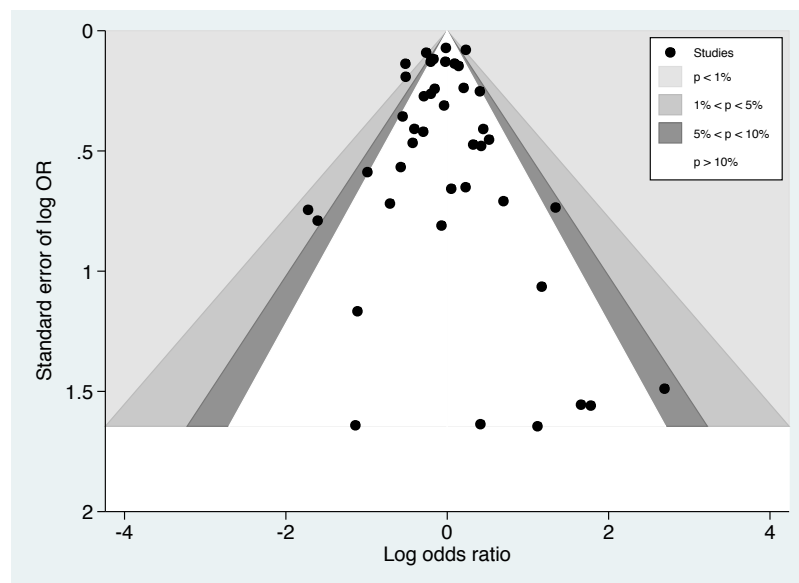
### (C) Major cerebrovascular events



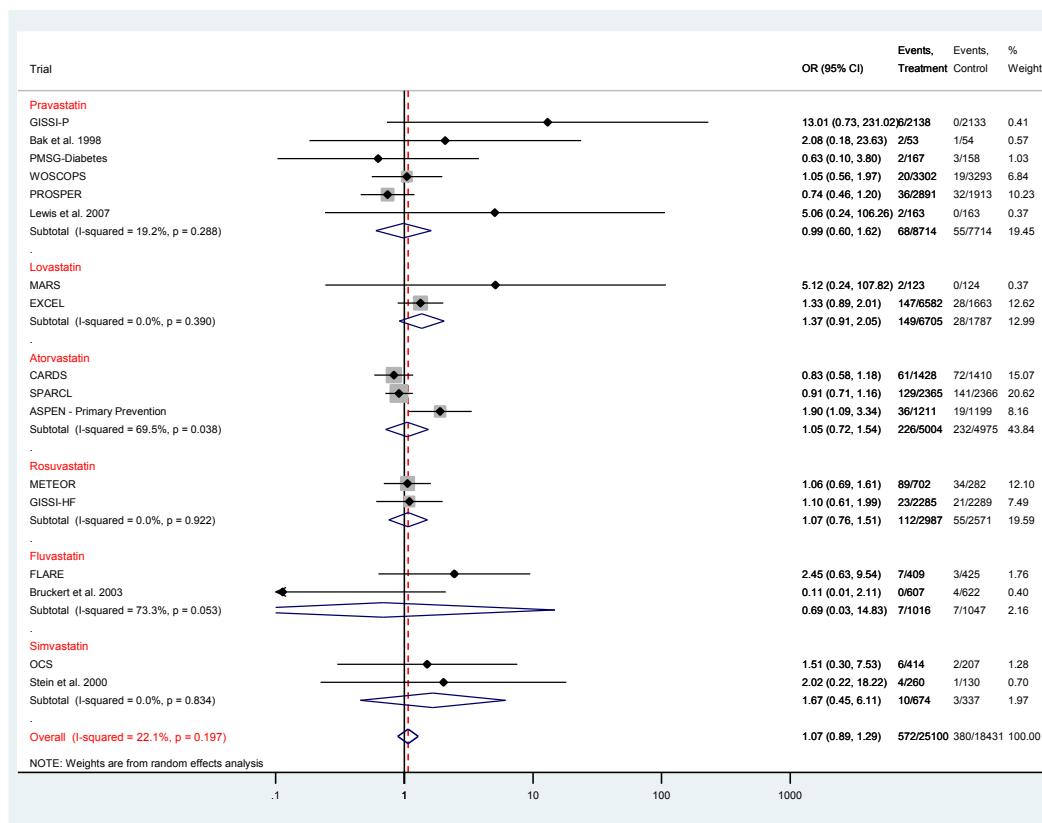


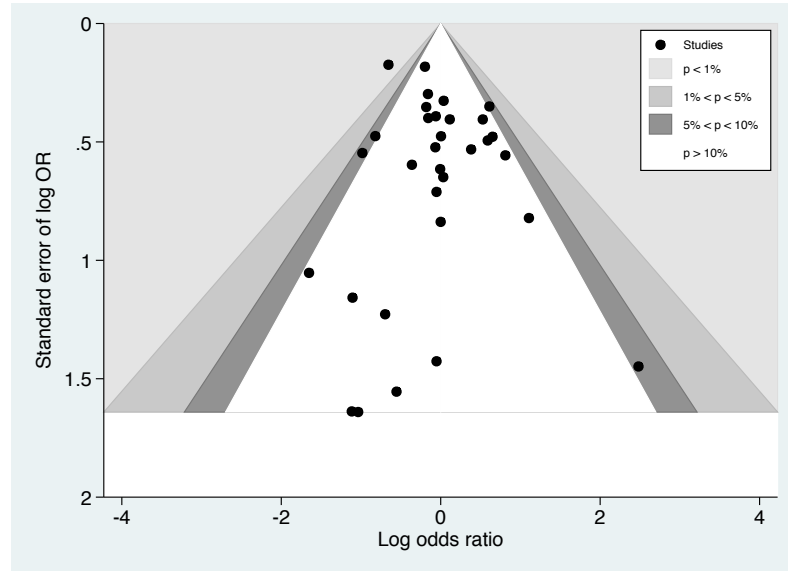
## (D) Discontinuations due to adverse events



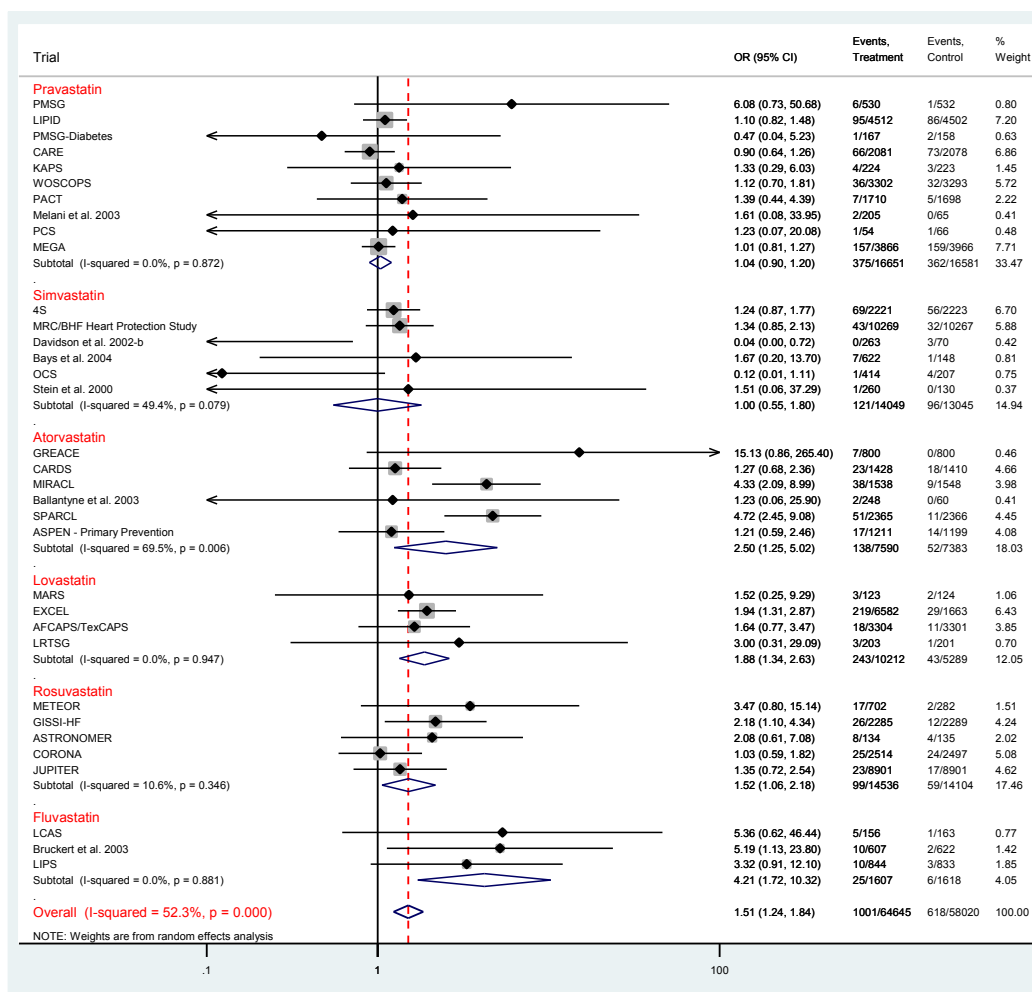


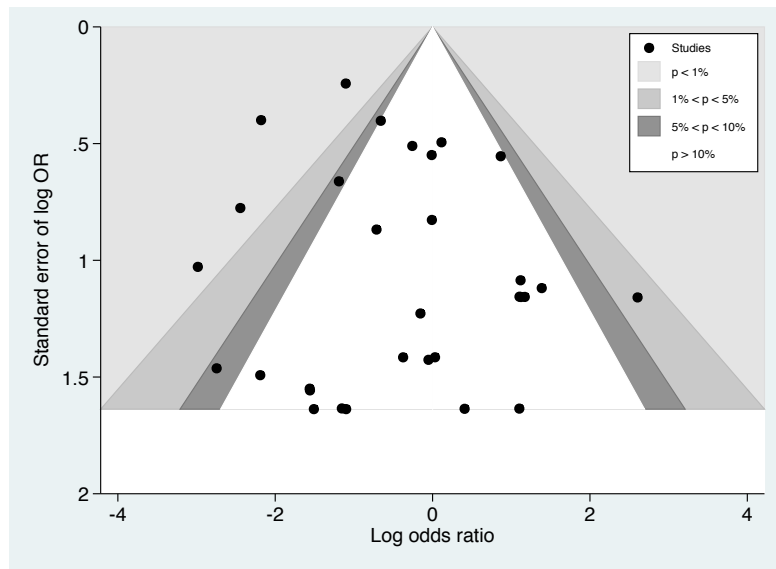
## (E) Myalgia



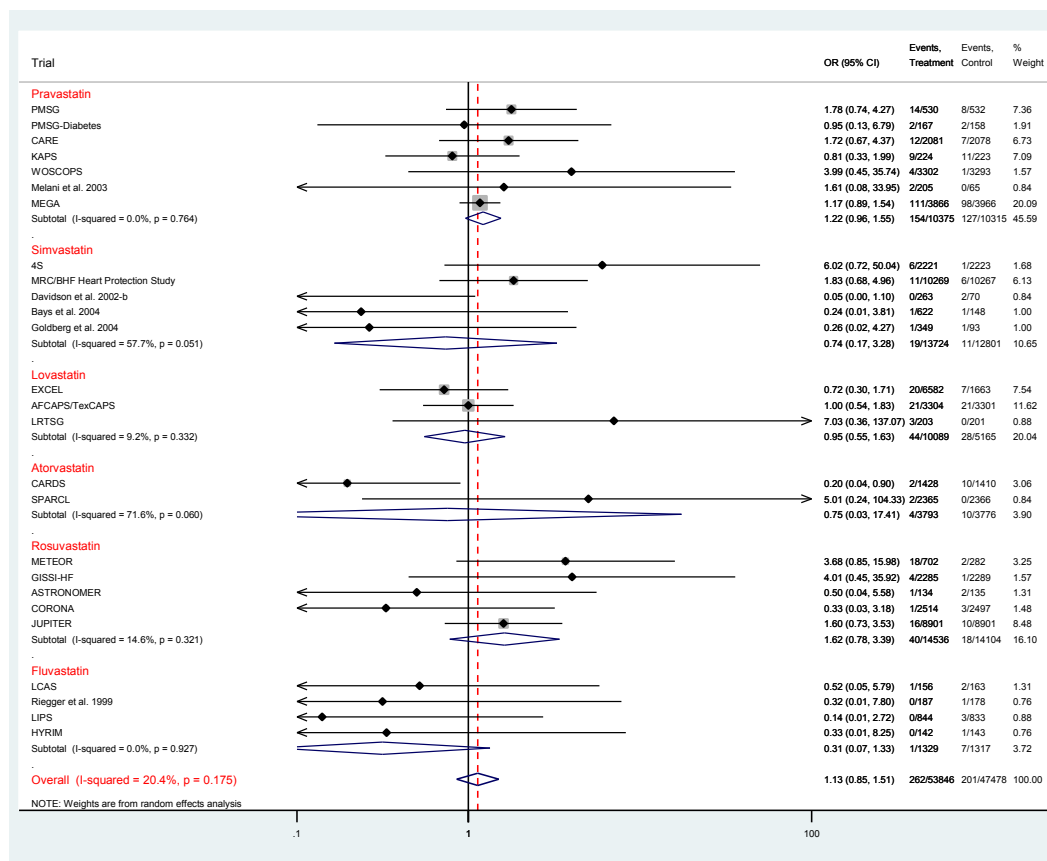


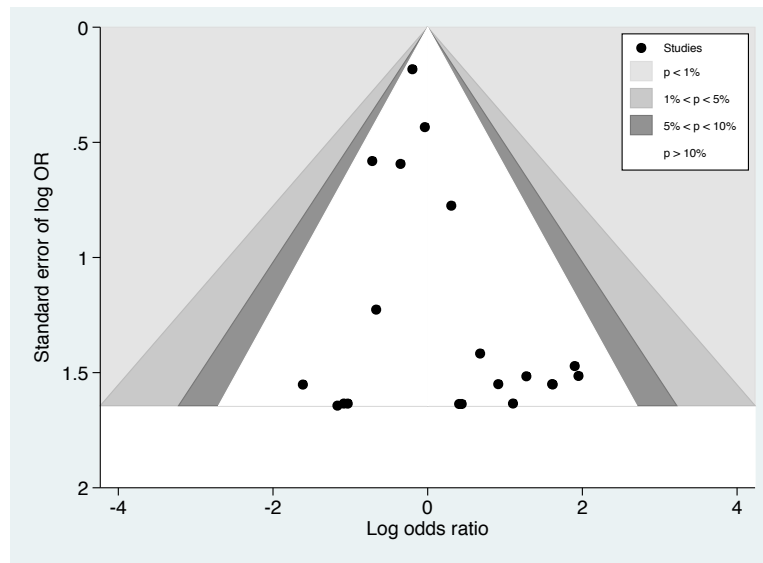
## (F) Transaminase elevations





## (G) Creatine kinase elevations

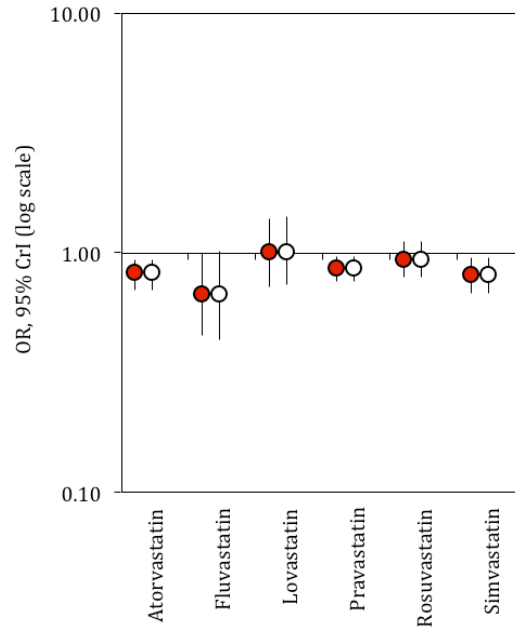




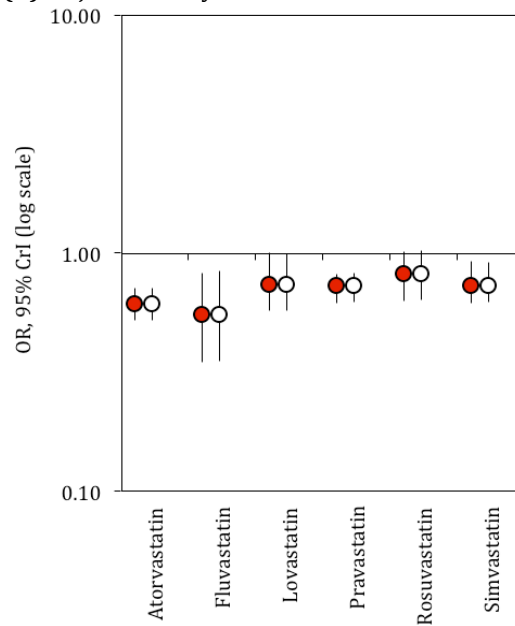
## **APPENDIX 5: Sensitivity of Primary Findings to Prior Distributions**

**Appendix Figure 2** – Sensitivity of network meta-analysis findings to prior distributions for between-trial heterogeneity. This figure shows the findings of sensitivity analyses by varying the prior distributions from less informative to more informative values and examining the variability observed in the credibility intervals of point estimates for **(A)** all-cause mortality, **(B)** major coronary event outcomes, **(C)** major cerebrovascular events, **(D)** discontinuations due to adverse events, **(E)** myalgia, **(F)** transaminase elevations, **(G)** creatine kinase elevations. Estimates shown in red were obtained from network meta-analyses using noninformative priors for between-trial heterogeneity [ $\sigma \sim \text{Uniform}(0,5)$ ]; estimates shown in white were obtained from network meta-analyses using more informative priors for between-trial heterogeneity [ $\sigma \sim \text{Uniform}(0,1)$ ].

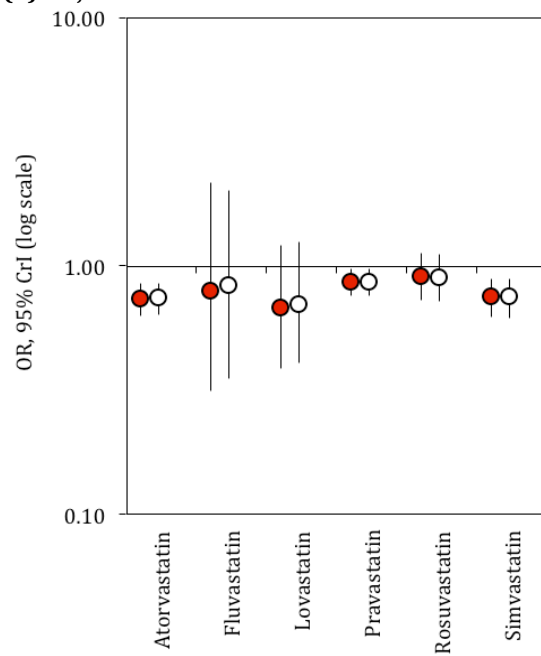
**(A)** All-cause mortality



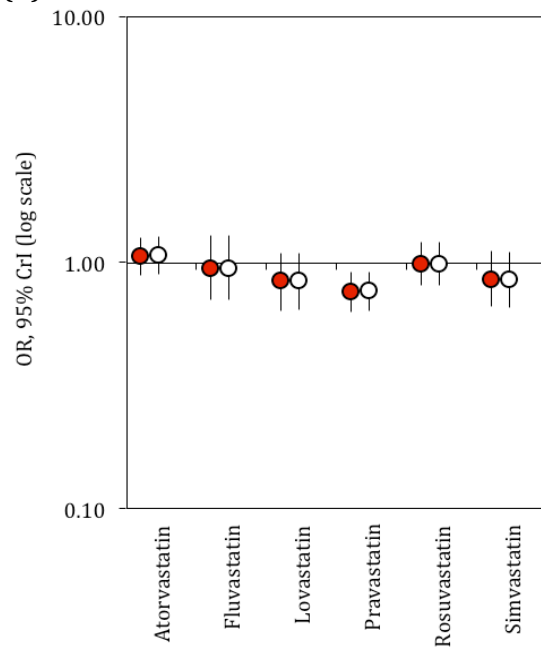
**(B)** Major coronary events

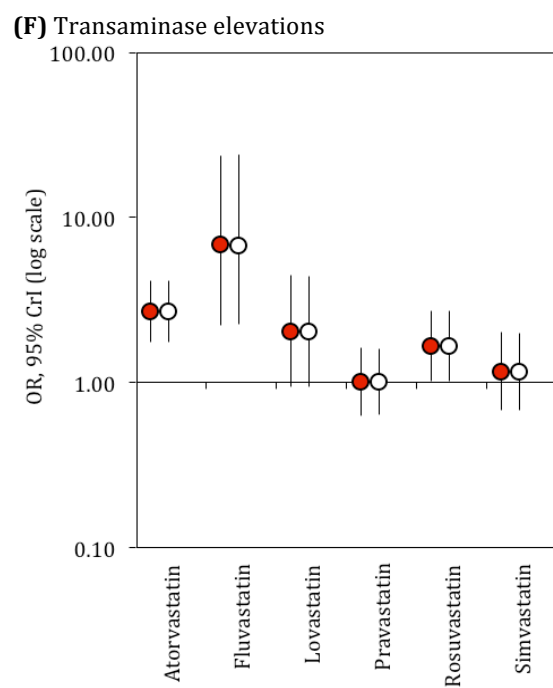
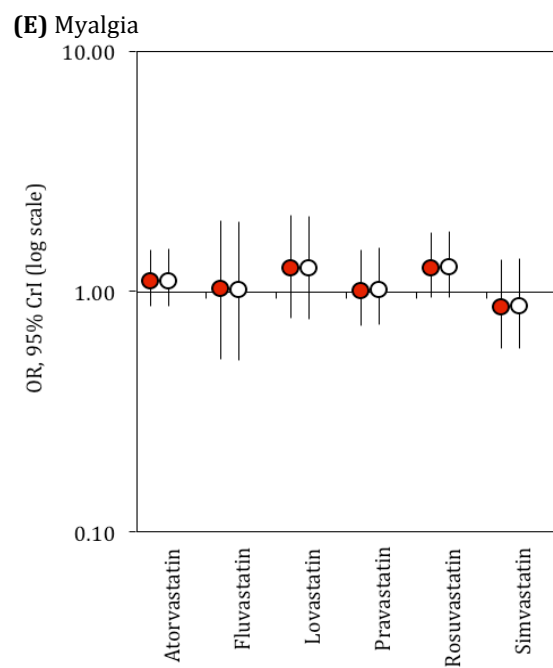


**(C)** Major cerebrovascular events

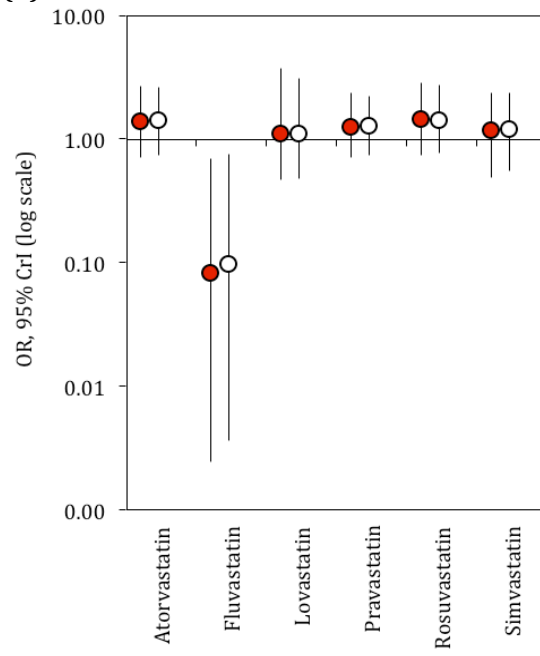


**(D)** Discontinuations due to adverse events





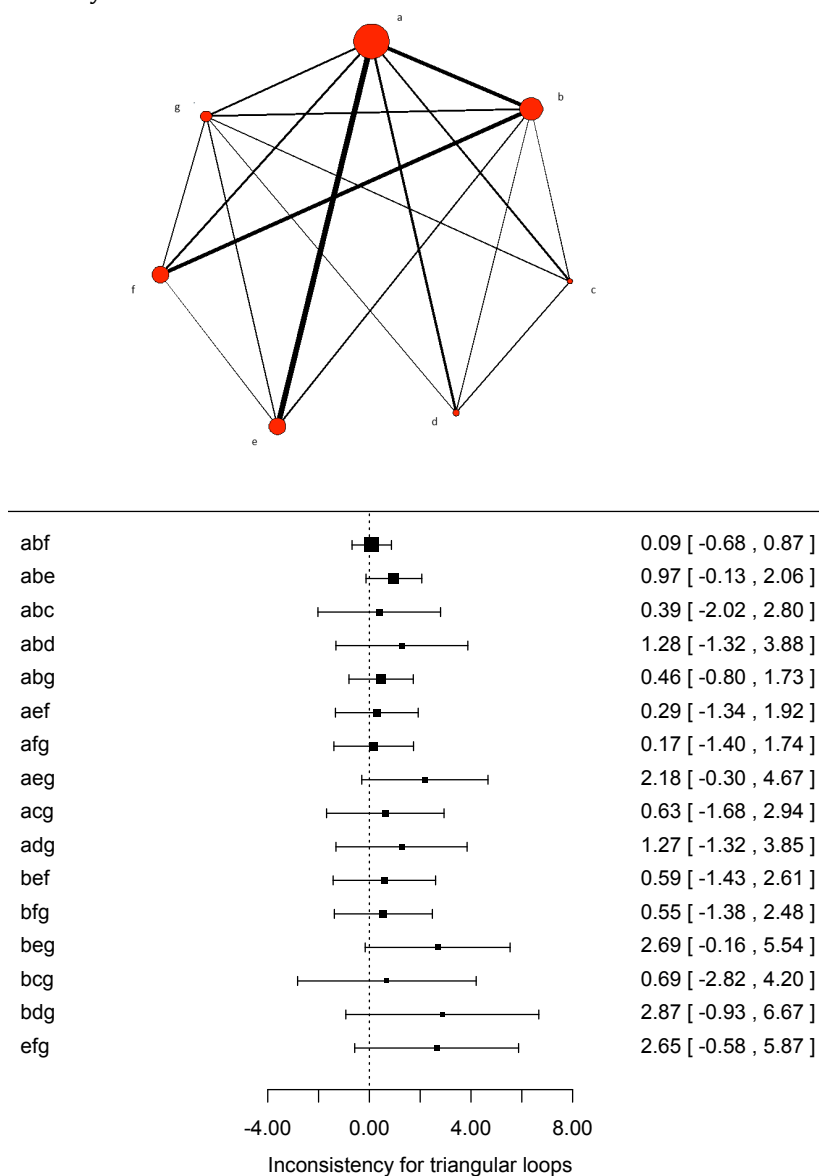
**(G)** Creatine kinase elevations



## **APPENDIX 6: Evaluation of Inconsistency**

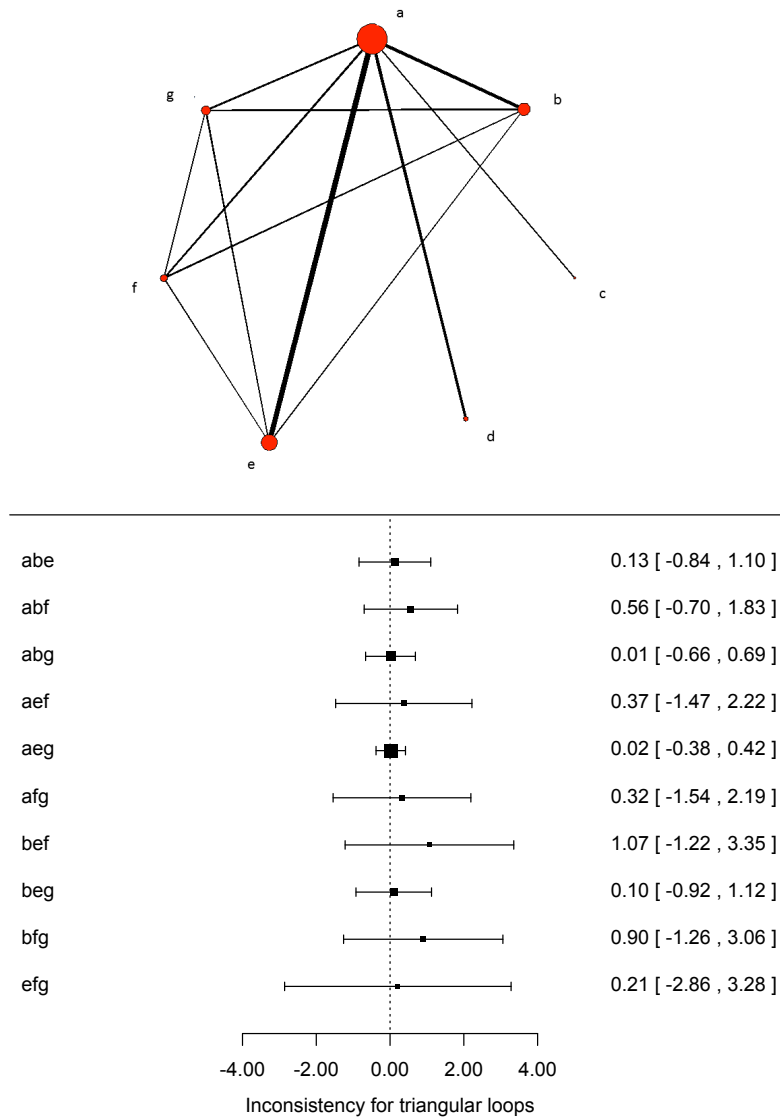
**Appendix Figure 3** – Statistical assessment of inconsistency in first-order loops in the treatment network for **(A)** all-cause mortality, **(B)** major coronary events, **(C)** major cerebrovascular events, **(D)** discontinuations, **(E)** myalgia, **(F)** transaminase elevations, and **(G)** creatine kinase elevations in placebo-controlled and active-comparator trials of participants with and without prior coronary heart disease at baseline (mixed patient population). In both (A) and (B), first figure shows all possible first-order loops (triangles) where both direct and indirect estimates could be obtained. Second figure shows the ratio of relative effects for indirect versus direct evidence. Inconsistency was defined as the disagreement between indirect and direct evidence with a 95% CI excluding 1.

**(A)** All-cause mortality



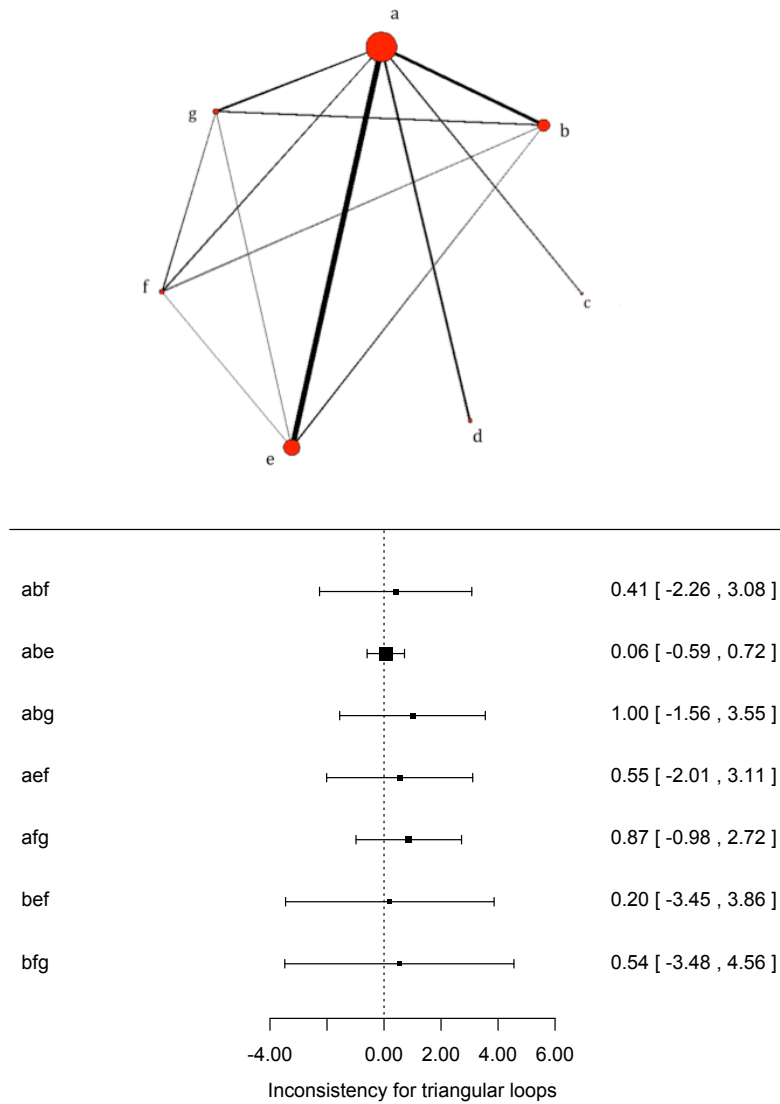
**Legend.** a: Control, b: Atorvastatin, c: Fluvastatin, d: Lovastatin, e: Pravastatin, f: Rosuvastatin, g: Simvastatin

**(B)** Major coronary events



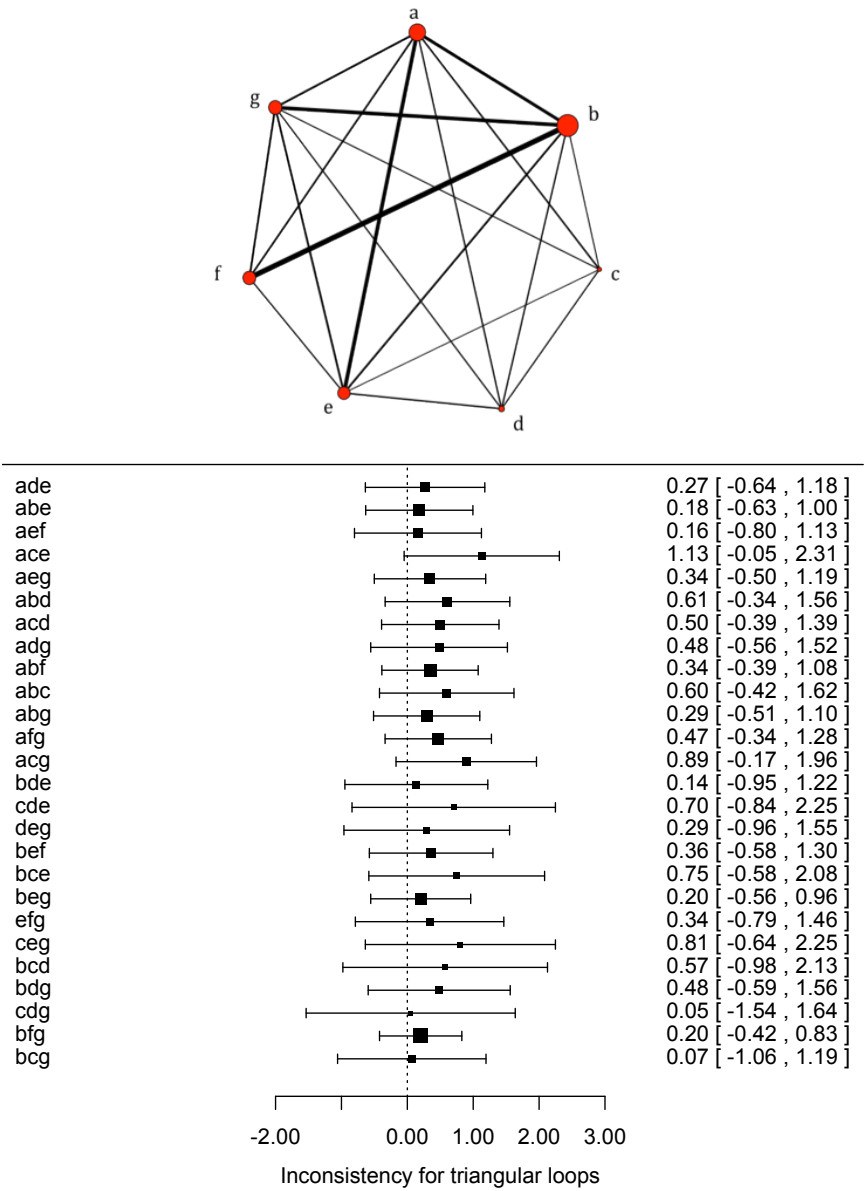
**Legend.** a: Control, b: Atorvastatin, c: Fluvastatin, d: Lovastatin, e: Pravastatin, f: Rosuvastatin, g: Simvastatin

**(C)** Major cerebrovascular events



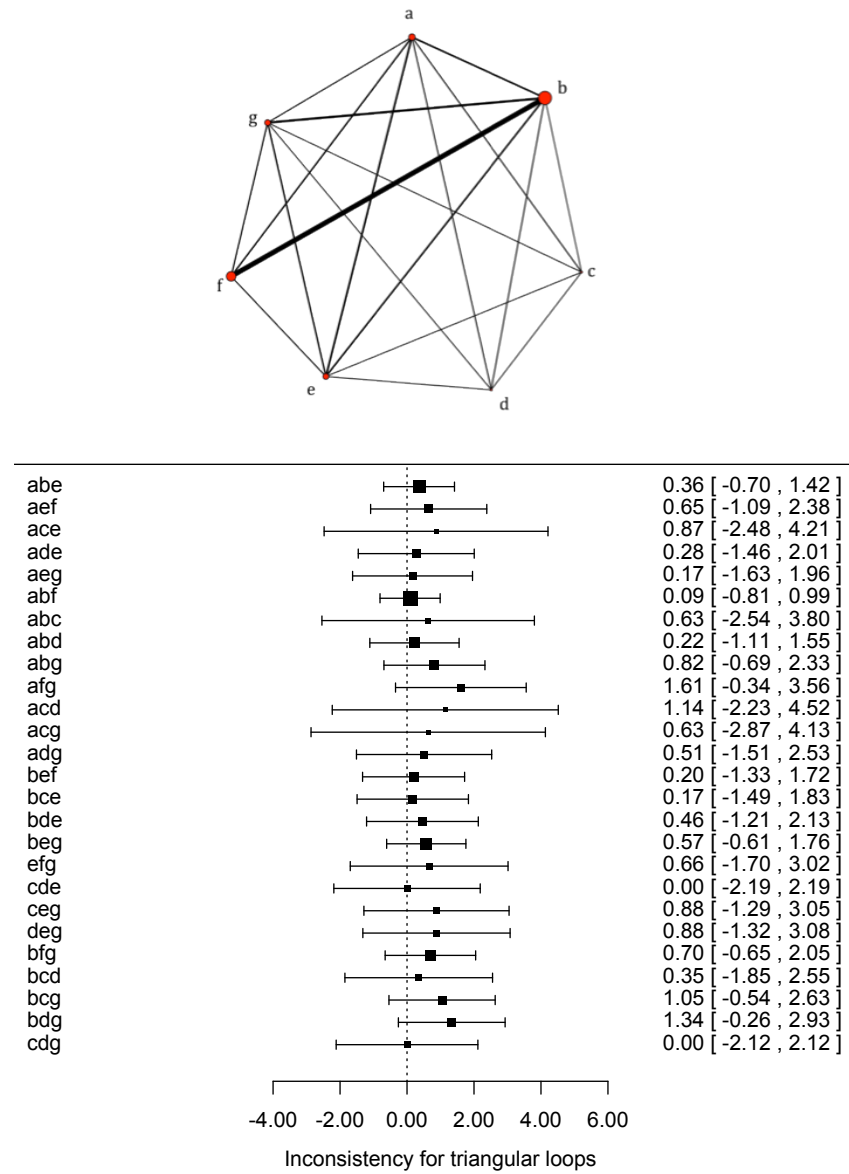
**Legend.** a: Control, b: Atorvastatin, c: Fluvastatin, d: Lovastatin, e: Pravastatin, f: Rosuvastatin, g: Simvastatin

(D) Discontinuities due to adverse events



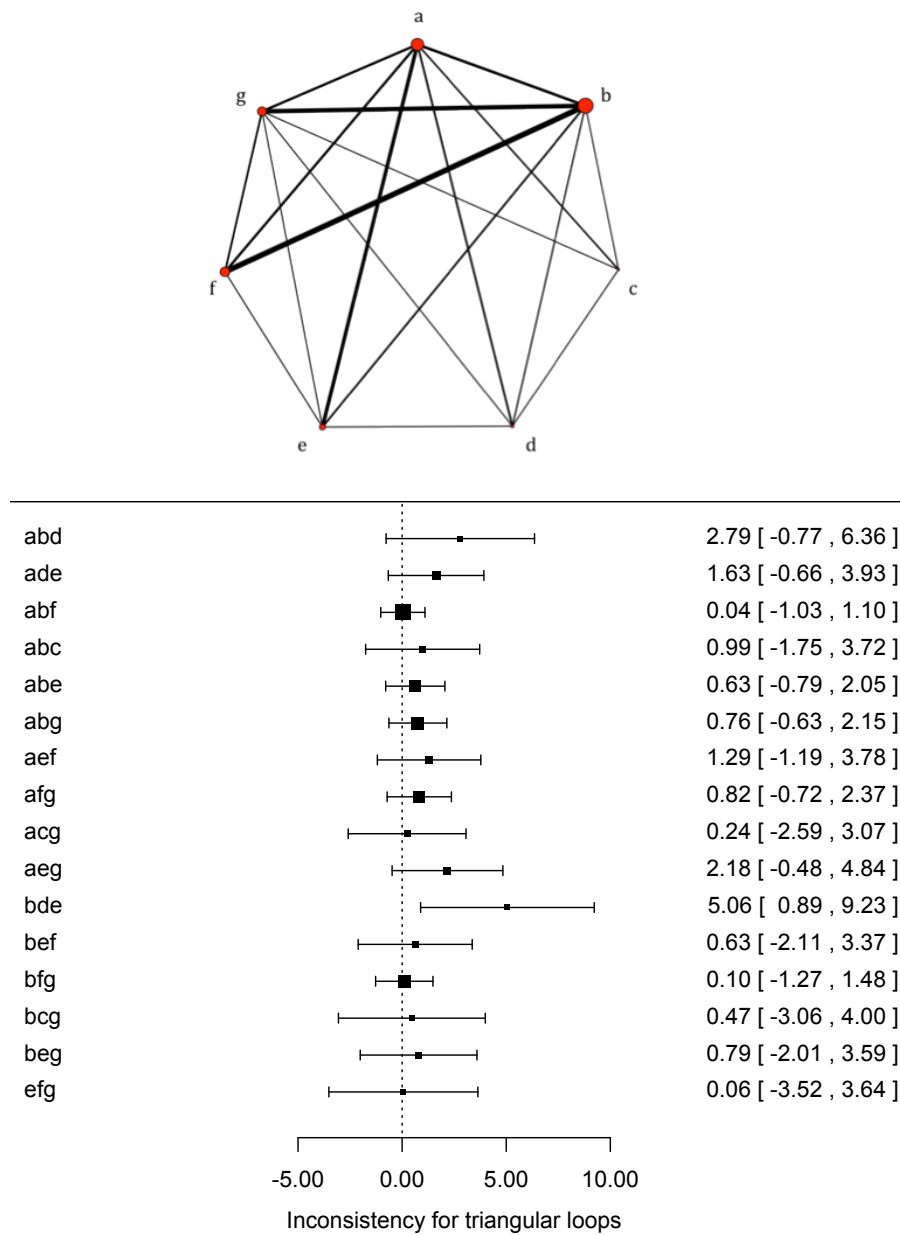
**Legend.** a: Control, b: Atorvastatin, c: Fluvastatin, d: Lovastatin, e: Pravastatin, f: Rosuvastatin, g: Simvastatin

**(E) Myalgia**



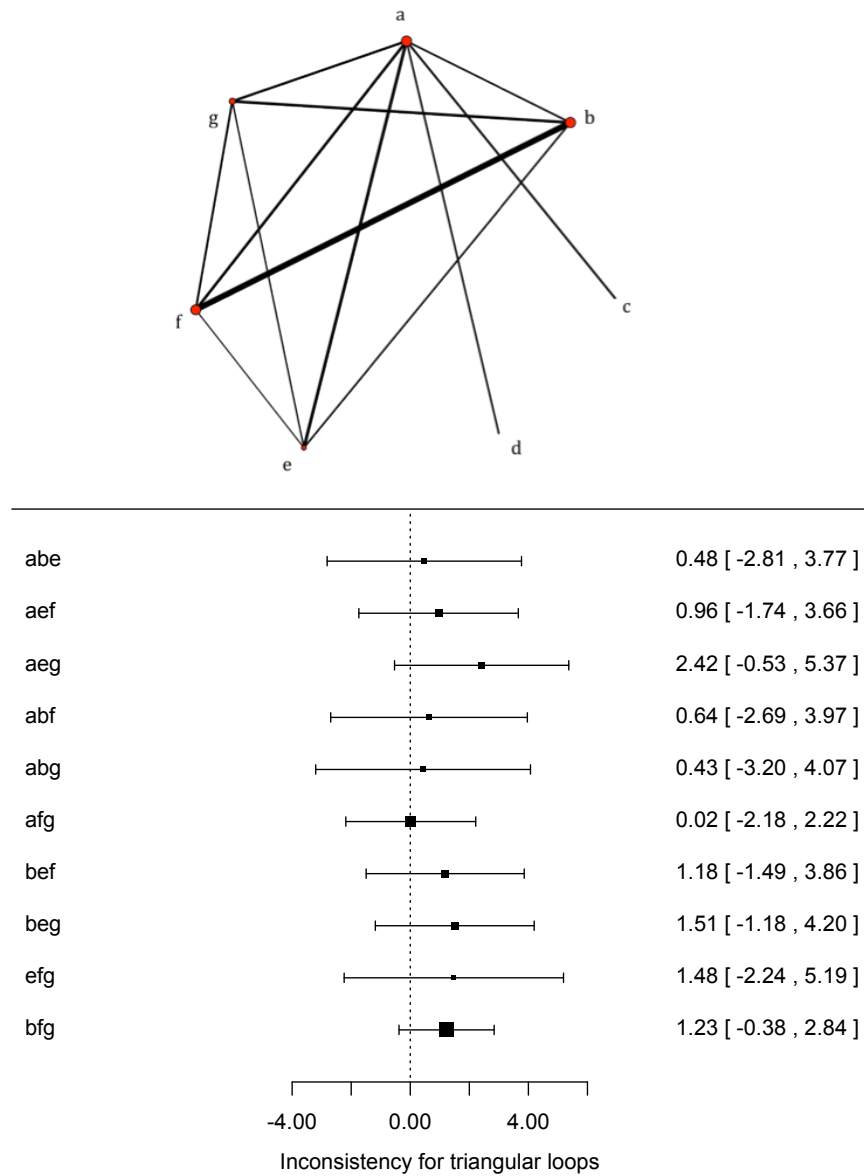
**Legend.** a: Control, b: Atorvastatin, c: Fluvastatin, d: Lovastatin, e: Pravastatin, f: Rosuvastatin, g: Simvastatin

**(F)** Transaminase elevations



**Legend.** a: Control, b: Atorvastatin, c: Fluvastatin, d: Lovastatin, e: Pravastatin, f: Rosuvastatin, g: Simvastatin

**(G)** Creatine kinase elevations



**Legend.** a: Control, b: Atorvastatin, c: Fluvastatin, d: Lovastatin, e: Pravastatin, f: Rosuvastatin, g: Simvastatin

## **APPENDIX 7: Published Articles**

# Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials

European Journal of Preventive  
Cardiology  
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Cardiology 2013  
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sagepub.co.uk/journalsPermissions.nav  
DOI: 10.1177/2047487313483600  
ejpc.sagepub.com  


Huseyin Naci<sup>1</sup>, Jasper J Brugts<sup>2</sup>, Rachael Florence<sup>3</sup> and  
AE Ades<sup>4</sup>

## Abstract

**Aims:** The extent to which individual statins vary in terms of their impact on serum lipid levels has been studied mainly on the basis of placebo-controlled trials. Our objective was to review and quantify the dose-comparative effects of different statins on serum lipid levels using both placebo- and active-comparator trials.

**Methods:** We systematically reviewed randomized trials evaluating different statins in participants with, or at risk of developing, cardiovascular disease. We performed random-effects Bayesian network meta-analyses to quantify the relative potency of individual statins across all possible dose combinations using both direct and indirect evidence. Dose-comparative effects were determined by estimating the mean change from baseline in serum lipids as compared to control treatment. (systematic review registration: PROSPERO 2011:CRD42011001470).

**Results:** We included 181 placebo-controlled and active-comparator trials including 256,827 individuals. There were 83 two-armed placebo-controlled trials and the remaining 98 were two- or multi-armed active-comparator trials. All statins reduced serum LDL and total cholesterol levels: higher doses resulted in higher reductions in pretreatment LDL and total cholesterol concentrations. In absolute terms, all statins significantly reduced LDL cholesterol levels as compared to control treatment from average baseline levels of approximately 150 mg/dl, except for fluvastatin at  $\leq 20$  mg/day and lovastatin at  $\leq 10$  mg/day. Atorvastatin, rosuvastatin, and simvastatin were broadly equivalent in terms of their LDL cholesterol-lowering effects. Dose-comparative effects of individual statins were not different between those with and without coronary heart disease at baseline. According to meta-regression analyses, LDL cholesterol-lowering effects of individual statins were not impacted by differences across trials in terms of baseline mean age and proportion of women as trial participants. Pretreatment LDL cholesterol concentrations had a marginally statistically significant effect on LDL cholesterol change from baseline. Mean differences from baseline in HDL cholesterol as compared to control treatment was not significant for any statin-dose combination.

**Conclusions:** The findings of this comprehensive review provide supporting evidence for the dose-response relationship of statins in reducing LDL and total cholesterol. The LDL cholesterol-reducing effects of some statins appear less pronounced than the findings of previous meta-analyses, which is particularly the case for the high-dose formulations of atorvastatin and rosuvastatin. The most consistent evidence for a combined reduction in both LDL and total cholesterol was achieved with atorvastatin at  $>40$  mg/day, rosuvastatin at  $>10$  mg/day, and simvastatin at  $>40$  mg/day, which appear equivalent in terms of their LDL and total cholesterol-reducing effects.

## Keywords

Statins, cholesterol, systematic review, meta-analysis, mixed treatment comparison, indirect comparison

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## Introduction

Statins effectively lower low-density lipoprotein cholesterol (LDL-C) and total cholesterol (Total-C), while resulting in modest increases in high-density lipoprotein cholesterol (HDL-C), reducing the risk of cardiovascular morbidity and mortality.<sup>1</sup> Clinical practice guidelines recommend using statins as the drugs of first choice in patients with hypercholesterolaemia or combined hyperlipidaemia.<sup>2</sup>

Dose-comparative effects of statins on serum lipid levels have been previously studied.<sup>3</sup> One of the most comprehensive of these studies, conducted by Law and colleagues,<sup>4</sup> was a meta-analysis of 164 short-term trials which typically lasted a few weeks and included approximately 24,000 individuals. Other examples include a review by Edwards and colleagues<sup>5</sup> that included double-blind trials that lasted longer than 12 weeks and included approximately 43,000 individuals. An important limitation of previous meta-analyses is that they relied solely on placebo-controlled trials without taking into account a large number of head-to-head trials which resulted in an enormous loss of valuable data. Although a limited number of direct (head-to-head) meta-analyses have been performed, these studies focused on two statins at a time – without a clear indication of the dose-comparative effects of all statins simultaneously.<sup>6,7</sup> For example, the comprehensive Drug Class Review included 102 head-to-head comparisons of different statins but did not perform a formal statistical analysis to estimate the pooled effects of each statin-dose combination and the statistical uncertainty around these estimates.<sup>1</sup> As previous studies have shown, qualitatively reviewing and comparing findings from different studies results in a biased interpretation of relative effectiveness.<sup>8</sup>

To date, there is no comprehensive analysis of the dose-comparative effects of statins that builds on the totality of the randomized trial evidence. This has important implications for clinical practice as clinicians do not have adequate evidence on the comparative effects of different statins on serum lipids based on direct head-to-head meta-analyses. Our objective in this study was to perform a systematic review of the statin literature and quantify the dose-comparative effects of statins on serum lipid levels by combining both placebo-controlled and active-comparator trials. Given the suboptimal lipid control in clinical practice,<sup>9–11</sup> this information is necessary as the foundation for evidence-based decision making.

In this paper, we report the findings of our multiple-treatments meta-analysis and meta-regression on the effect of different statins on serum LDL-C, Total-C, and HDL-C levels. By doing so, we address the following questions: What is the estimated lipid change from

baseline that can be expected with various doses of different statins? Is the estimated lipid change from baseline sensitive to patient characteristics such as age, sex, baseline LDL-C concentration, and pre-existing coronary heart disease?

## Methods

### Systematic review

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials to identify studies published between 1 January 1985 and 1 January 2011. To identify the relevant literature, we developed a search strategy using the search terms atorvastatin, fluvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, cholesterol, cardiovascular disease, and hydroxymethylglutaryl-CoA reductase inhibitors/therapeutic use. We also performed manual searches using the authors' files and reference lists from original communications and review articles to cross check references. Two researchers (BT, HT) independently performed abstract, title, and full-text screening. A third researcher approved study selection (HN).

We included open-label and double-blind randomized controlled trials comparing one statin with another at any dose or with control (placebo, diet, or usual care) for adults with, or at risk of developing, cardiovascular disease. We included trials of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin if they had more than 50 participants per trial arm, lasted longer than 4 weeks, and reported one of the three surrogate outcomes of interest: LDL-C, HDL-C, or Total-C. Both fixed-dose and titration designs were included. Per pre-defined criteria, we excluded trials conducted in patients with renal insufficiency.

Whenever possible, we categorized included trials as primary prevention, secondary prevention, or mixed patient population. Trials that included at least 80% of participants without established coronary heart disease or reported data separately on a sole primary prevention group were categorized as primary prevention. Trials that included at least 80% of participants with established coronary heart disease or reported data separately on a sole secondary prevention group were categorized as secondary prevention. All remaining trials were categorized as having a mixed patient population.

The primary outcome of interest was the mean change from baseline in serum LDL-C levels between two comparator treatments for a given dose (change from baseline in the treatment group minus that in the control group). Secondary outcomes were HDL-C and Total-C levels between two comparator treatments

for a given dose. We used a structured form developed in MS Excel to extract data on trial and patient population characteristics, and outcomes. A full list of data extraction elements can be found in our publicly available protocol.<sup>12</sup> One researcher extracted data (HN) and another independently checked for accuracy (BT).

### Statistical analysis

We first qualitatively summarized included trials, describing the types of direct and indirect comparisons and important clinical and methodological variables. To determine the comparative effects of statins at different doses, we conducted network meta-analyses, which are generalizations of indirect comparisons with more than two (or multiple pairs of) treatments being compared indirectly and at least one pair of treatments compared both directly and indirectly.<sup>13,14</sup> This type of analysis allowed for combining the direct within-trial comparisons between two treatments (e.g. atorvastatin vs. control) with indirect comparisons constructed from trials that had one treatment in common (e.g. atorvastatin vs. control and simvastatin vs. control).<sup>15</sup> This analysis preserved the within-trial randomized treatment comparison of each trial while combining all available comparisons between treatments. We combined study-level relative treatment effects using Bayesian Markov chain Monte Carlo methods in WinBUGS version 1.4.3.<sup>16</sup> We used the model developed by Dias and colleagues<sup>17</sup> for the National Institute of Health Clinical Excellence Decision Support Unit in the UK. This was based on modelling the outcomes in every treatment group of every study and specifying the relations among the relative effects across studies making different comparisons, while taking into account the correlations between treatment effects within multi-arm trials.

Both fixed- and random-effects models were run. The fixed-effects model assumed that there was no between-study heterogeneity. The random-effects model took into account potential heterogeneity by assuming that each treatment at each dose was drawn from the same distribution, whose mean and variance were estimated from the data.<sup>18</sup> Model fit was better with the random-effects model (for the primary outcome, the total residual deviance for the random-effects model was 216.4 for 214 unconstrained data points as compared to 219.1 for the fixed-effects model) and only the results from the random-effects model are presented.

The difference between treatments was assessed on the basis of 95% credible intervals (CI), which may be interpreted as Bayesian equivalents of 95% confidence intervals. The 95% CI can be interpreted as indicating a 95% probability that the true mean change falls within

this range. If a 95% CI does not include the null value 0.00, this can be interpreted as indicating <5% probability that there is no difference between the two comparators. Given the Bayesian nature of the statistical analyses, *p*-values are not provided.

We assessed the probability that each statin-dose combination is best by calculating its treatment effect compared with control treatment, and counting the proportion of iterations for which each statin has the highest treatment effect, the second highest, and so on. This approach took into account the magnitude of the estimated treatment effect as well as the uncertainty around it. We developed rankograms and cumulative probability plots to graphically present the distribution of ranking probabilities, and estimated the surface under the cumulative ranking line for each statin.<sup>19</sup> The surface under the cumulative ranking line for each statin would be 1.0 (or 100%) when a treatment is certain to be the best and 0.0 (0%) when a treatment is certain to be the worst.

To obtain a comprehensive estimate of the comparative effect of statins at different doses on serum lipid levels, our network meta-analysis pooled all primary and secondary prevention trials in addition to trials with mixed patient populations, including all placebo-controlled and active-comparator trials eligible for inclusion in this review. For the primary outcome of LDL-C changes from baseline, we also performed separate analyses for the primary and secondary prevention populations, as categorized by the criteria mentioned above.

Trials that allowed variable dosing regimens (titrating) were included in the statistical analysis. Whenever possible, data from the fixed dosing period were used for titration designs. If all patients were force-titrated to a given dosage, data from the final high-dose period were used. Where trials provided data on the proportion of patients at different doses, the number in the treatment arm was proportioned out to the correct dosage.

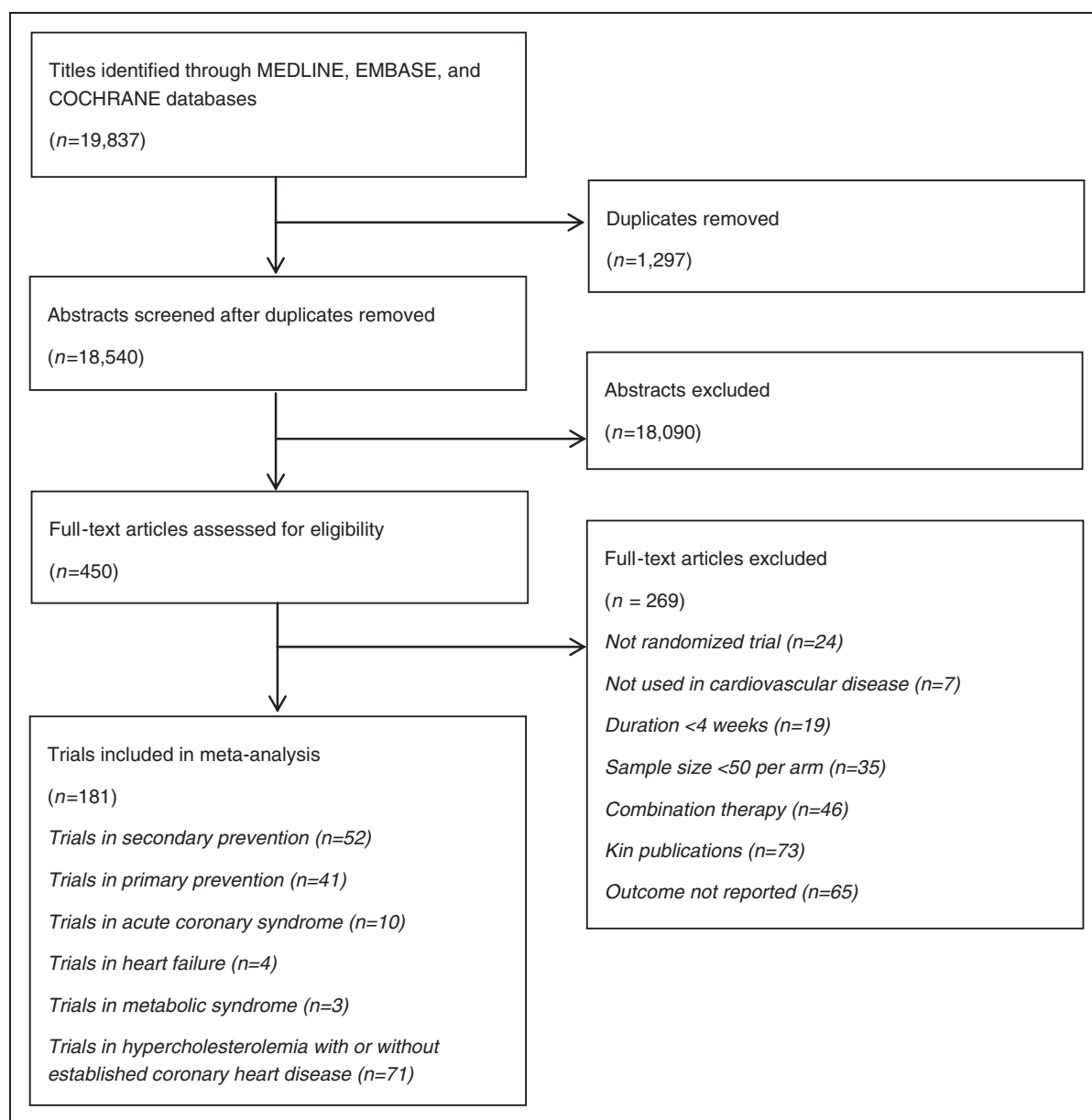
All analyses were dose-specific and explored the effects of individual statins at different doses separately. Each statin-dose combination was treated as a different treatment and no trends were fitted or assumed. The following daily doses were considered for atorvastatin, lovastatin, pravastatin, and simvastatin: ≤10 mg (10), 11–20 mg (20), 21–40 mg (40), and >40 mg (80). For fluvastatin, daily doses were ≤20 mg (20), 21–40 mg (40), and >40 mg (80). For rosuvastatin, the daily doses were ≤5 mg (5), 6–10 mg (10), >11–20 mg (20), and >20 mg (40).  $\chi^2$  test for linear trend was performed to test for the linearity of the dose-response relationship. All analyses were based on the total number of randomly assigned participants regardless of whether the study authors perform intention-to-treat analyses.

We investigated whether potential heterogeneity and inconsistency across the evidence base in the network meta-analysis could be explained by mean age at baseline, mean LDL-C concentration at baseline, or the proportion of women included in the trial using meta-regression analyses. We performed all meta-regression analyses by allowing for a common treatment-covariate interaction for each statin compared to control.<sup>20</sup> We also qualitatively evaluated the consistency of relative treatment effects obtained from an analysis of head-to-head trials (i.e. direct evidence) with those obtained from an analysis combining both placebo-controlled and active-comparator trials (i.e. mixed evidence).

We visually inspected the consistency of the relative treatment effects for potential differences between estimates obtained from two sets of analyses (i.e. direct and mixed estimates).

## Results

We included 181 trials (Figure 1, see supplementary material for references of included trials and trial and population characteristics, available online only). There were 83 two-armed placebo-controlled trials and the remaining 98 were two- or multi-armed active-comparator trials, and 112 trials were double-blind



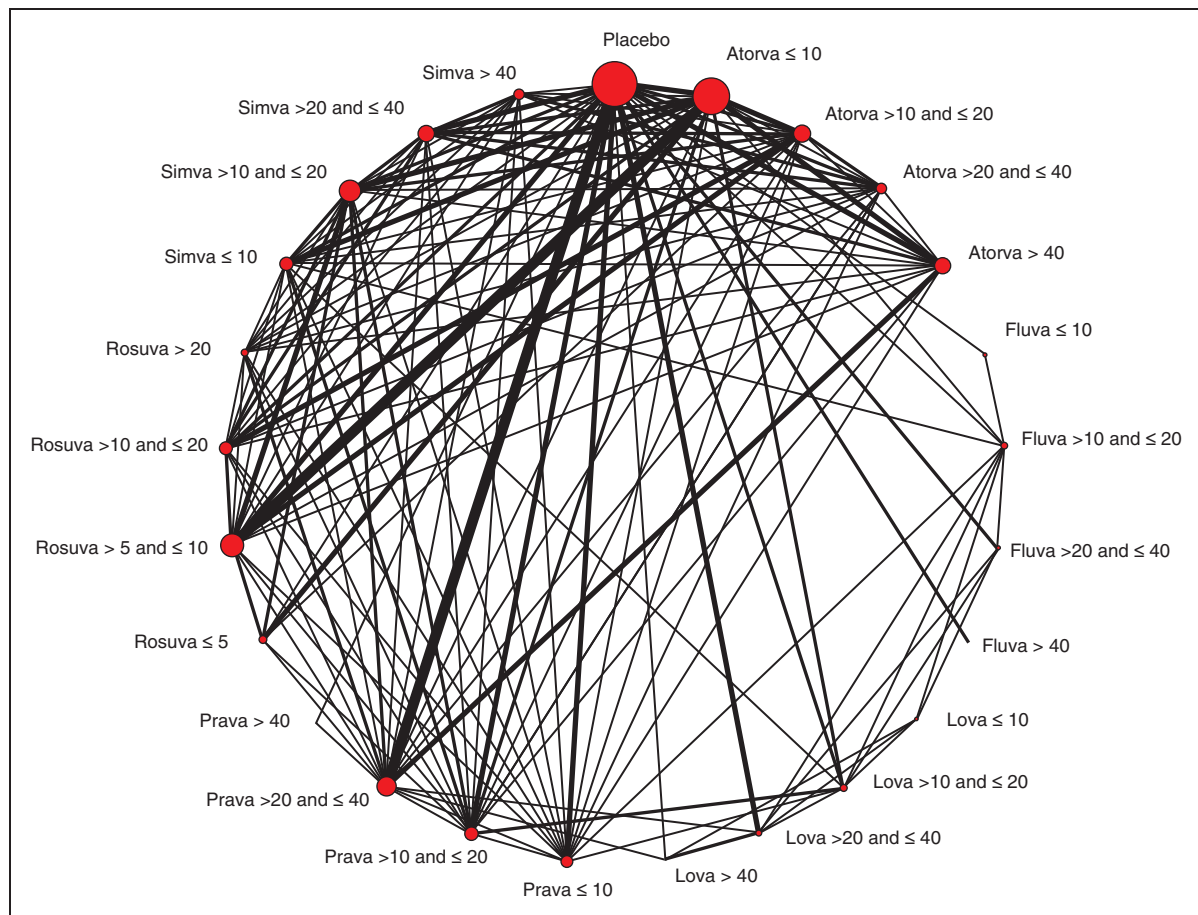
**Figure 1.** Flow diagram of trial identification and selection.

while 55 were open-label and two were single-blind. Blinding was not clear for the remaining 12 trials. Overall, the average trial duration was 66 weeks, with 53 trials reporting serum lipid levels after at least 1 year of follow up. Figure 2 shows the network of eligible comparisons when all populations were pooled. Most frequent comparisons occurred between pravastatin and placebo, and rosuvastatin and atorvastatin. No trial directly compared all statin-dose combinations to each other.

Differential dose-comparative effects of individual statins on serum lipid levels are shown in Figure 3 and Table 1. Figure 4 shows the estimated percentage reductions from an average baseline concentration of 150 mg/dl (3.88 mmol/l, approximate average of pretreatment LDL-C level in included trials). Regarding LDL-C reduction, higher statin doses were associated with greater relative reductions in pretreatment LDL-C ( $\chi^2$  test for linear trend for all statins except for rosuvastatin in lowering LDL-C:  $p < 0.00$ ; rosuvastatin:  $p = 0.08$ ). Similarly, except for lovastatin ( $p = 0.09$ ) and pravastatin

( $p = 0.11$ ), there was a general linear dose-response relationship for reducing Total-C from baseline as compared to control. According to the network meta-analysis results, atorvastatin, pravastatin, rosuvastatin, and simvastatin were significantly better than control treatment in terms of reducing baseline concentrations of LDL-C. However, fluvastatin (at  $\leq 40$  mg/day) and lovastatin (at  $\leq 10$  mg/day) did not result in significant reductions from baseline LDL-C levels as compared to control treatment. Considering Total-C reduction, fluvastatin (at all doses), lovastatin (at  $\leq 10$  mg/day and 21–40 mg/day), and pravastatin (at  $> 40$  mg/day) did not have adequate evidence to demonstrate superiority over control treatment in terms of lowering pretreatment levels. Statin-dose combinations resulted in only modest increases in baseline HDL-C levels, and were not significantly better than control treatment. Higher doses of statins were not associated with greater increases in baseline HDL-C concentrations.

Figure 5 shows the dose-comparative effects of individual statins on pretreatment LDL-C levels in primary



**Figure 2.** Network of available comparisons. Connecting lines indicate the direct pair-wise comparison between two treatments. The width of the lines is proportional to the number of pair-wise comparisons between two treatments, and the size of every node is proportional to the number of participants.

and secondary prevention populations separately. Generally, higher statin doses were associated with greater relative reductions in pretreatment LDL-C but this dose response relationship was not as clear as in the base-case analysis including all populations. With greatly overlapping 95% credible intervals, there was no statistical difference between the LDL-C-reducing effects of individual statins between populations with and without coronary heart disease at baseline.

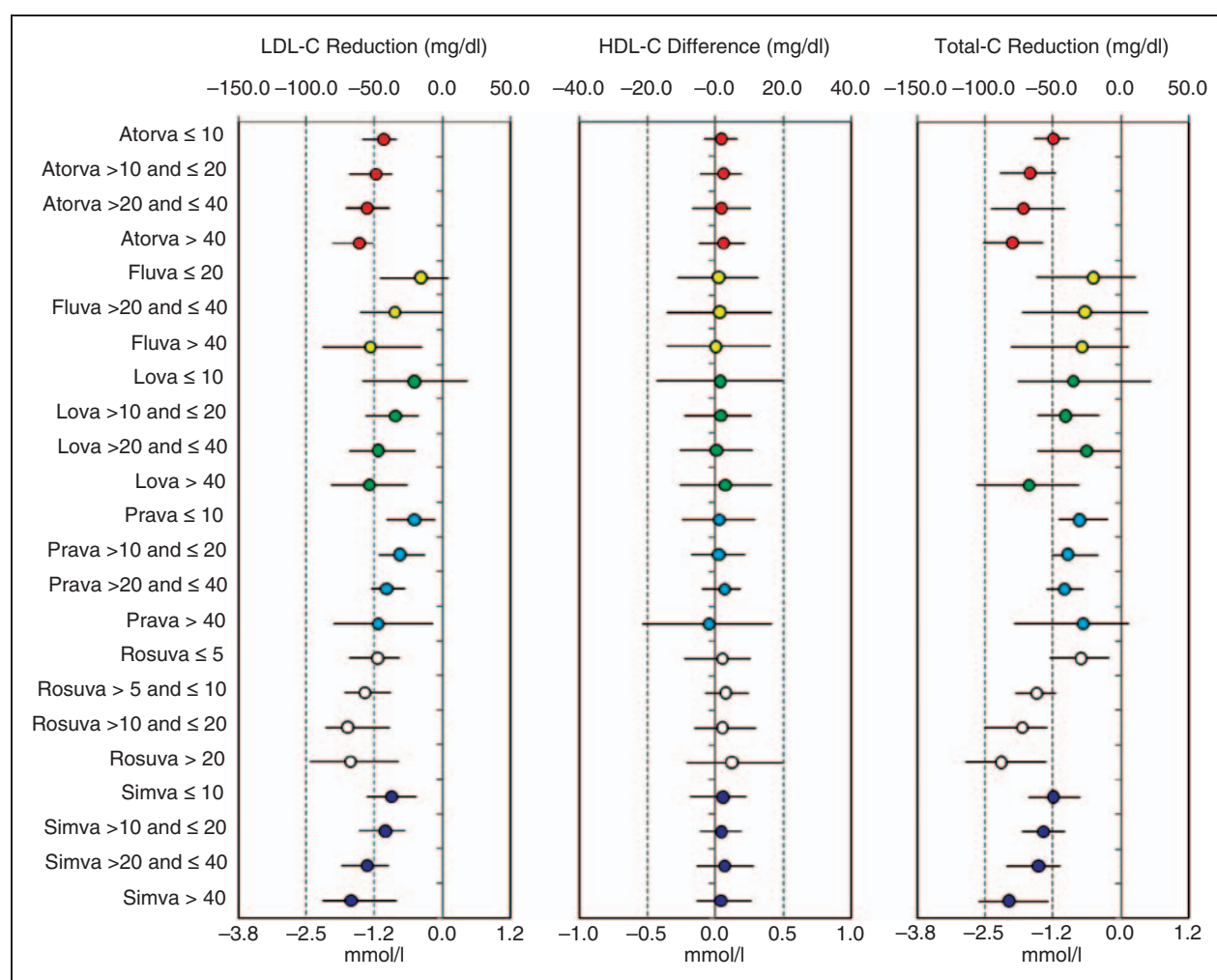
Figure 6 shows the ranking of individual statin-dose combinations in terms of lowering both baseline LDL-C and Total-C concentrations. Ranking first, simvastatin (>40 mg/day), atorvastatin (>40 mg/day), and rosuvastatin (>10 mg/day) resulted in the highest reductions in baseline LDL-C and Total-C concentrations as compared to other statins.

Figure 7 reports the findings from all three sets of meta-regression analyses. According to the meta-

regression analyses, baseline mean age ( $\beta = 0.54$ , 95% CI  $-0.76$ ,  $2.13$ ) and proportion of women included in the trials ( $\beta = 0.05$ , 95% CI  $-0.43$ ,  $0.60$ ) did not explain heterogeneity in the analysis. Baseline mean LDL-C concentration was marginally statistically significant ( $\beta = -0.23$ , 95% CI  $-0.49$ ,  $-0.05$ ) but its impact on the reduction of pretreatment LDL-C concentrations in meta-regressions were not materially different. Also, there was no detectable inconsistency between direct and indirect estimates. Between-study heterogeneity was low (standard deviation =  $1.71$ , 95% CI  $0.25$ ,  $4.64$ ).

## Discussion

This network meta-analysis of 256,827 individuals demonstrates the dose-comparative effects of individual statins on serum lipid concentrations. Overall, high-dose statins were associated with greater reductions in



**Figure 3.** Dose-comparative effects of statins on serum lipid levels.

Values are mean (95% credible interval). Estimates shown are mean changes from baseline in serum lipid concentrations as compared to control treatment. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Total-C, total cholesterol; atorva, atorvastatin; fluva, fluvastatin; lova, lovastatin; prava, pravastatin; rosuva, rosuvastatin; simva, simvastatin.

**Table 1.** Dose-comparative effects of statins on serum lipid levels in serum lipid LDL-C, HDL-C, and Total-C concentrations

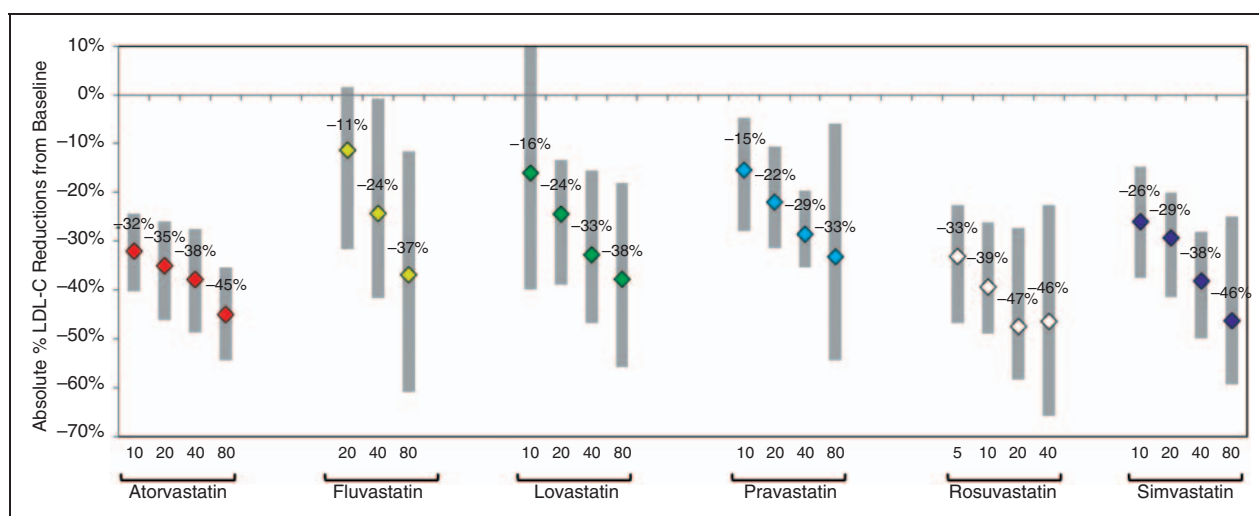
Dose	≤5	6–10	11–20	21–40	>40
Low-density lipoprotein cholesterol					
Atorvastatin					
mg/dl	–	–43.16 (–58.77, –34.08)	–48.33 (–67.89, –36.77)	–54.79 (–70.88, –38.63)	–60.82 (–80.06, –50.86)
mmol/l	–	–1.11 (–1.51, –0.88)	–1.24 (–1.75, –0.95)	–1.41 (–1.83, –0.99)	–1.57 (–2.07, –1.31)
Fluvastatin					
mg/dl	–	–	–15.46 (–45.66, 4.62)	–34.51 (–60.29, 0.62)	–52.80 (–87.54, –15.10)
mmol/l	–	–	–0.39 (–1.18, 0.11)	–0.89 (–1.55, 0.01)	–1.36 (–2.26, –0.39)
Lovastatin					
mg/dl	–	–20.33 (–57.98, 18.02)	–34.37 (–56.22, –17.54)	–47.15 (–68.26, –20.21)	–53.41 (–81.61, –25.38)
mmol/l	–	–20.33 (–57.98, 18.02)	–34.37 (–56.22, –17.54)	–47.15 (–68.26, –20.21)	–53.41 (–81.61, –25.38)
Pravastatin					
mg/dl	–	–20.41 (–40.62, –4.98)	–31.12 (–45.85, –12.91)	–40.77 (–51.68, –27.00)	–47.14 (–79.49, –7.10)
mmol/l	–	–0.52 (–1.05, –0.12)	–0.80 (–1.18, –0.33)	–1.05 (–1.33, –0.69)	–1.21 (–2.05, –0.18)
Rosuvastatin					
mg/dl	–47.37 (–68.37, –31.64)	–56.85 (–71.45, –37.59)	–69.24 (–85.59, –38.81)	–67.54 (–96.74, –32.46)	–
mmol/l	–1.22 (–1.76, –0.81)	–1.47 (–1.84, –0.97)	–1.79 (–2.21, –1.00)	–1.74 (–2.50, –0.83)	–
Simvastatin					
mg/dl	–	–36.98 (–54.78, –19.25)	–41.69 (–60.71, –27.42)	–54.92 (–74.13, –39.91)	–66.87 (–87.66, –33.99)
mmol/l	–	–0.95 (–1.41, –0.49)	–1.07 (–1.56, –0.70)	–1.42 (–1.91, –1.03)	–1.72 (–2.26, –0.87)
High-density lipoprotein cholesterol					
Atorvastatin					
mg/dl	–	2.01 (–2.89, 6.41)	2.38 (–4.47, 7.76)	1.88 (–6.57, 10.35)	2.58 (–4.51, 8.78)
mmol/l	–	0.05 (–0.07, 0.16)	0.06 (–0.11, 0.20)	0.04 (–0.16, 0.26)	0.06 (–0.11, 0.22)
Fluvastatin					
mg/dl	–	–	1.03 (–10.77, 12.58)	1.33 (–14.28, 16.65)	0.27 (–14.22, 16.23)
mmol/l	–	–	0.02 (–0.27, 0.32)	0.33 (–0.36, 0.43)	0.00 (–0.36, 0.41)
Lovastatin					
mg/dl	–	1.48 (–17.17, 19.72)	1.76 (–8.80, 10.52)	0.36 (–10.15, 10.89)	3.00 (–10.16, 16.47)
mmol/l	–	0.03 (–0.44, 0.50)	0.04 (–0.22, 0.27)	0.00 (–0.26, 0.28)	0.07 (–0.26, 0.42)
Pravastatin					
mg/dl	–	1.23 (–9.43, 11.65)	1.10 (–6.93, 8.81)	2.81 (–3.77, 7.30)	–1.63 (–21.24, 16.61)
mmol/l	–	0.03 (–0.24, 0.30)	0.02 (–0.17, 0.22)	0.07 (–0.09, 0.18)	0.04 (–0.54, 0.42)
Rosuvastatin					
mg/dl	2.15 (–8.81, 10.40)	3.16 (–2.81, 9.79)	2.16 (–5.94, 12.03)	4.91 (–8.24, 19.86)	–
mmol/l	0.05 (–0.22, 0.26)	0.08 (–0.07, 0.25)	0.05 (–0.15, 0.31)	0.12 (–0.21, 0.51)	–
Simvastatin					
mg/dl	–	2.39 (–7.37, 8.89)	1.79 (–4.25, 7.66)	2.77 (–5.30, 11.43)	1.69 (–5.32, 10.56)
mmol/l	–	0.06 (–0.19, 0.22)	0.04 (–0.10, 0.19)	0.07 (–0.13, 0.29)	0.04 (–0.13, 0.27)
Total cholesterol					
Atorvastatin					
mg/dl	–	–49.49 (–63.63, –37.82)	–66.75 (–88.38, –47.49)	–71.55 (–94.70, –41.28)	–79.22 (–101.20, –57.75)
mmol/l	–	–1.27 (–1.64, –0.97)	–1.72 (–2.28, –1.22)	–1.85 (–2.44, –1.06)	–2.04 (–2.61, –1.49)
Fluvastatin					
mg/dl	–	–	–19.82 (–61.95, 10.99)	–26.27 (–72.20, 20.00)	–28.41 (–80.73, 5.70)
mmol/l	–	–	–0.51 (–1.60, 0.28)	–0.67 (–1.86, 0.51)	–0.73 (–2.08, 0.14)
Lovastatin					
mg/dl	–	–34.66 (–75.46, 22.64)	–40.21 (–60.72, –16.24)	–24.94 (–60.82, –0.54)	–67.26 (–105.60, –30.90)
mmol/l	–	–0.89 (–1.95, 0.58)	–1.03 (–1.57, –0.41)	–0.64 (–1.57, –0.01)	–1.73 (–2.73, –0.79)
Pravastatin					
mg/dl	–	–30.07 (–44.94, –9.58)	–38.61 (–50.52, –17.02)	–41.16 (–54.05, –27.39)	–27.28 (–77.76, 6.41)
mmol/l	–	–0.77 (–1.16, –0.24)	–0.99 (–1.30, –0.44)	–1.06 (–1.39, –0.70)	–0.70 (–2.01, 0.16)

(continued)

Table 1. Continued

Dose	≤5	6–10	11–20	21–40	>40
Rosuvastatin					
mg/dl	–29.03 (–52.01, –8.91)	–61.49 (–77.06, –47.58)	–72.14 (–100.20, –54.28)	–87.75 (–113.9, –55.32)	–
mmol/l	–0.75 (–1.34, –0.23)	–1.59 (–1.99, –1.23)	–1.86 (–2.59, –1.40)	–2.26 (–2.94, –1.43)	–
Simvastatin					
mg/dl	–	–49.48 (–67.77, –30.16)	–56.93 (–72.62, –40.93)	–60.26 (–83.73, –44.15)	–81.94 (–103.90, –53.73)
mmol/l	–	–1.27 (–1.75, –0.77)	–1.47 (–1.87, –1.05)	–1.55 (–2.16, –1.14)	–2.11 (–2.68, –1.38)

Values are mean (95% credible interval). Estimates shown are mean changes from baseline as compared to control treatment.



**Figure 4.** Dose-comparative effects of statins on serum LDL-C concentrations.

Values are mean (95% credible interval). Estimates shown are absolute reductions at all dose combinations standardized to the average pretreatment LDL-C concentration in the included set of trials.

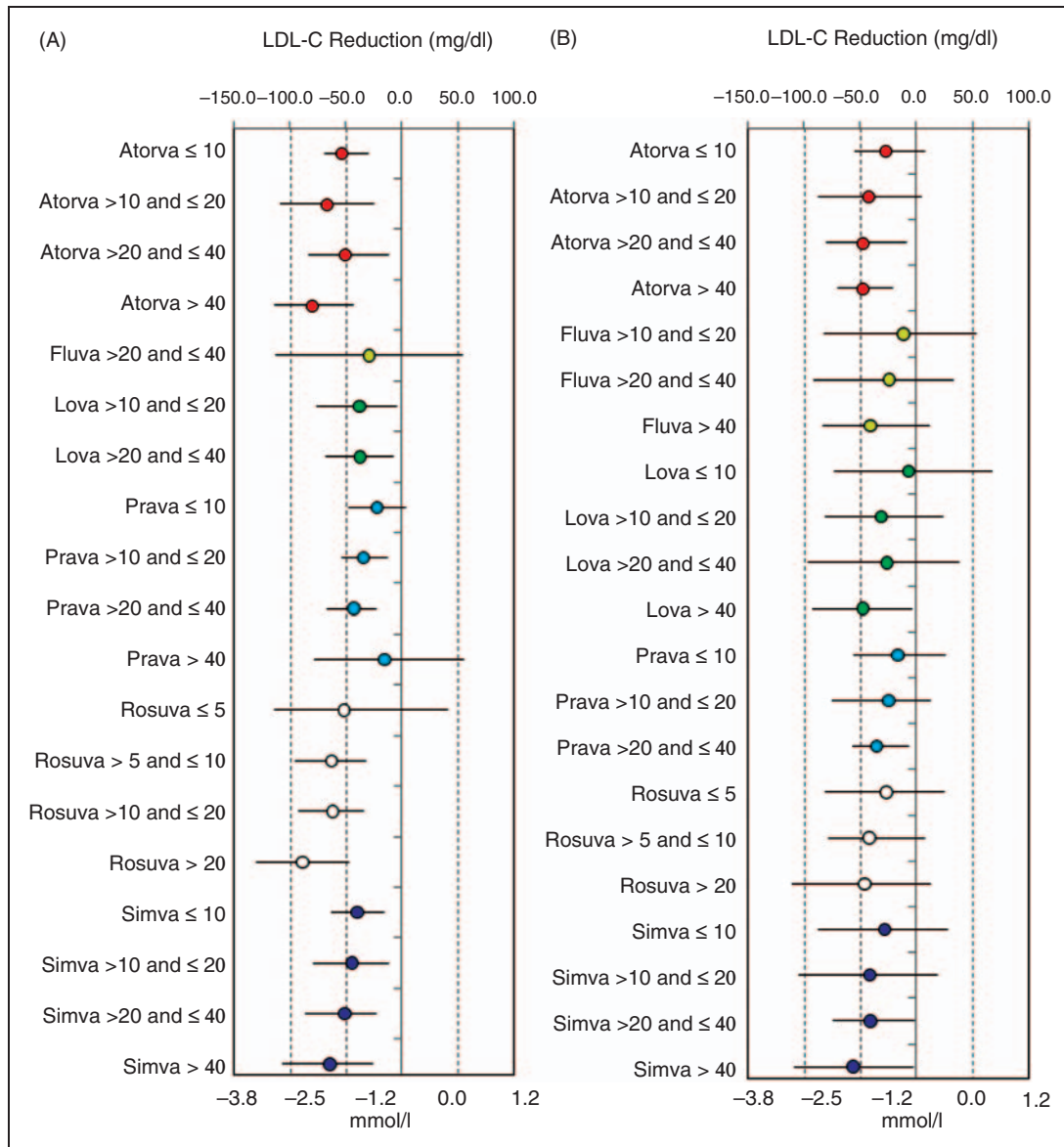
pretreatment LDL-C and Total-C concentrations as compared to low-dose regimens. In terms of increasing HDL-C, all statin-dose combinations failed to result in clinically and statistically meaningful increases in pretreatment HDL-C levels and higher doses were not associated with better HDL improvements.

When individual statins were compared head-to-head, several statins appeared to outperform other statins in reducing serum LDL-C and Total-C concentrations. In our meta-analysis, atorvastatin, rosuvastatin and simvastatin ranked first in terms of reducing serum LDL-C and Total-C as compared to the other statins. High-dose formulations of atorvastatin, rosuvastatin, and simvastatin were broadly equivalent. Fluvastatin, lovastatin, and pravastatin, on the other hand, were associated with significantly less reductions in pretreatment LDL-C and Total-C concentrations relative to other statins. Low-dose regimens of fluvastatin and lovastatin did not lower pretreatment cholesterol levels over and above the reduction observed in control treatment.

This analysis is the first to quantitatively evaluate the dose-comparative effects of different statins on serum lipids across all populations. Previous comprehensive reviews such as the Drug Class Review did not perform statistical analyses. The statin dose conversion/equivalence tables that stem from previous reviews do not take into account the statistical uncertainty around the dose-comparative effects of statins. As a result, existing dose conversion tables give the false impression that prescribers should expect narrow ranges of LDL-C reductions at various statin doses.

Based on our findings, we developed a revised 'Statin Prescribing Reference' table (Table 2) to report the statistically equivalent doses of statins and the percentage LDL-C changes that can be expected when prescribing them. Also included are statements about the consistency of the evidence associated with the preferred agents, which reflect the variability (and uncertainty) in the evidence base.

The findings of our analysis are novel and differ from previous reviews in important ways. First, the



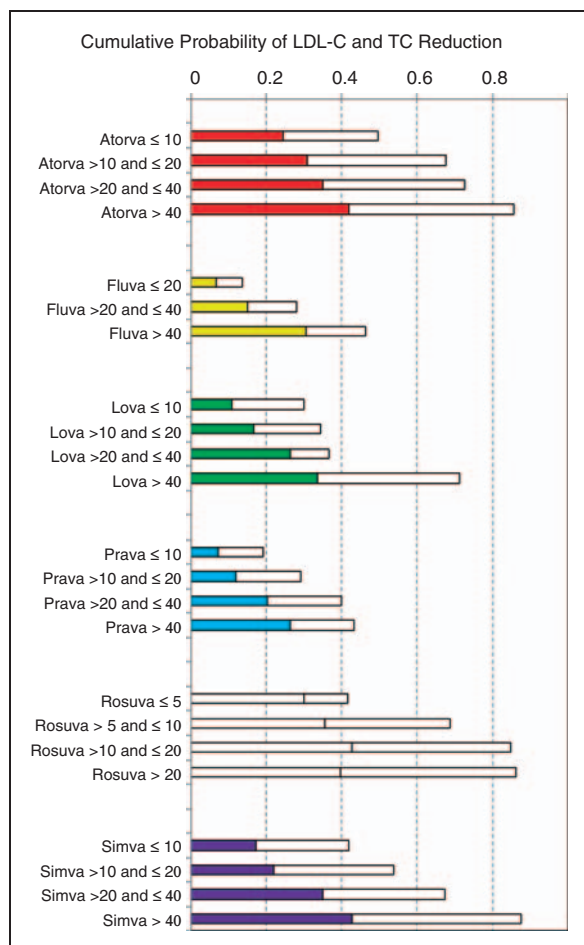
**Figure 5.** Sub-group analysis results.

Values are mean (95% credible interval). Estimates shown are mean changes from baseline in LDL-C concentrations as compared to control treatment. Results are provided separately for primary prevention (A) and secondary prevention (B) populations.

LDL-C, low-density lipoprotein cholesterol; atorva, atorvastatin; fluva, fluvastatin; lova, lovastatin; prava, pravastatin; rosuva, rosuvastatin; simva, simvastatin.

traditionally considered ‘more powerful’ statins notably rosuvastatin which is not generic, and atorvastatin which has recently been released as a generic – are not found to be statistically superior to simvastatin in their maximum LDL-C-lowering doses. Second, the extent to which some statins lower pretreatment LDL-C levels appears to be less pronounced in our review compared to earlier estimates. This was particularly the case for atorvastatin and rosuvastatin at high doses. For instance, according to previous analyses, high-dose atorvastatin (at 80 mg/day) lowers pretreatment LDL-C levels by 55% (and 60% according to manufacturer’s

prescribing information).<sup>1,4,21</sup> We found that high-dose atorvastatin lowers baseline LDL-C concentrations by an estimated 45% (95% CI 35, 54%). Similarly, according to manufacturer’s prescribing information, high-dose rosuvastatin lowers pretreatment LDL-C levels by 63%. However, the findings of our analysis suggested that high-dose rosuvastatin resulted in a 46% mean reduction from baseline, which was associated with considerable uncertainty (95% CI 23, 66%). This difference was also observed for other statin-dose combinations: 20 mg/day of fluvastatin (–22% per prescribing information vs. –11% in our analysis), 20 mg/day of



**Figure 6.** Dose-comparative ranking and equivalence of statins in terms of both LDL-C and Total-C reduction.

Estimates shown are based on the surface under the cumulative ranking (SUCRA) plots by combining LDL-C (left-part of the stacked bars) and Total-C (right-part of the stacked bars) -reducing effects of individual statins. Statin-dose combinations are ranked out of a total of 1.0 (0.5 for LDL-C and 0.5 for Total-C). LDL-C, low-density lipoprotein cholesterol; Total-C, total cholesterol; atorva, atorvastatin; fluva, fluvastatin; lova, lovastatin; prava, pravastatin; rosuva, rosuvastatin; simva, simvastatin.

pravastatin (−32% per prescribing information vs. −22% in our analysis). LDL-C-lowering effects of simvastatin according to our analyses appeared consistent with previous findings.

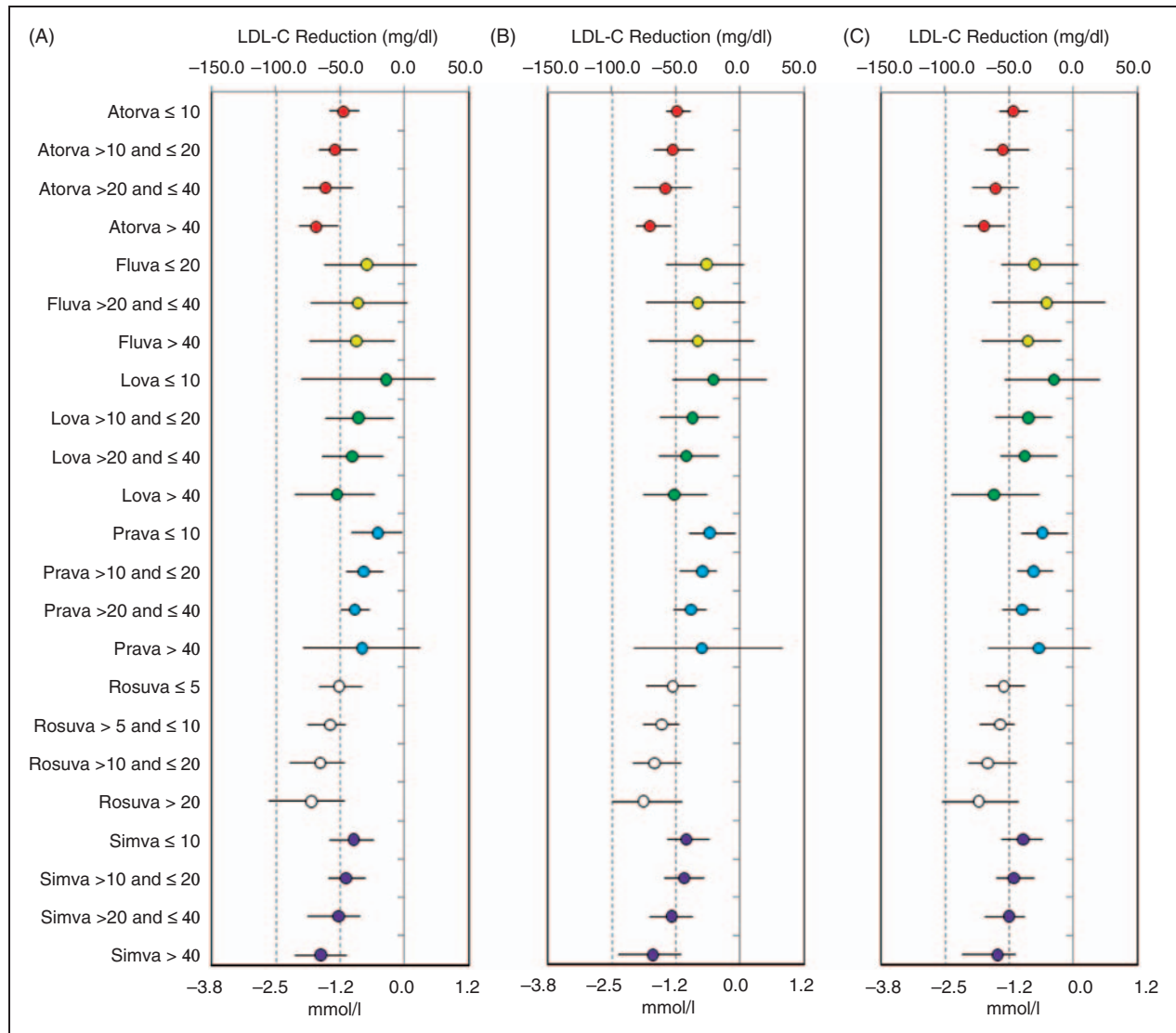
We attribute this difference to three main factors. First, previous assessments of dose-comparative effects of statins were based on small studies, which tend to evaluate highly-selected patients in strictly controlled environments, which may not be representative of the conditions in actual clinical practice. Our review excluded trials that included fewer than 50 individuals per trial arm. Second, unlike previous reviews, our review included trials with individuals regardless of

their baseline LDL-C concentrations. Third, earlier reviews excluded trials with titration designs. Titration designs allowing clinicians to increase the dose of statin therapy to achieve target reductions, also known as the ‘treat-to-target’ model, continues to be the most common method of managing patients with elevated LDL cholesterol levels. Accordingly, we included information from titration design trials.

Our analysis combined direct and indirect evidence and compared all available statin-dose combinations. This methodology differs from traditional pair-wise meta-analysis in that it combines placebo-controlled and active-comparator trials, facilitating the comparison of multiple interventions.<sup>22</sup> Increasingly used to compare more than two health interventions simultaneously, network meta-analyses provide information that can be used to rank treatments, which helps clinicians, patients, and other healthcare decisionmakers when making prescribing decisions.<sup>23</sup> We previously used this methodology to compare the benefits of individual statins in the primary and secondary prevention of all-cause mortality,<sup>24</sup> major coronary events, and major cerebrovascular events.<sup>25</sup>

The findings of our analysis should be interpreted in light of its limitations. First, our review did not evaluate the comparative costs and harms of individual statins, which should be taken into consideration when making prescribing decisions.<sup>26</sup> This is particularly important given our finding that generic statins such as simvastatin perform equally well as other branded statins in terms of lowering pretreatment LDL-C levels. There is a paucity of evidence on the comparative harms of individual statins. Future studies should focus on addressing this important gap in the literature. Equally important, there are other important lipid outcomes, which should be evaluated in future analyses.<sup>27</sup> For instance, recent analyses have shown the association between non-HDL cholesterol levels with the risk of cardiovascular events among patients treated with statin therapy.<sup>28</sup>

Second, our literature-based meta-analysis shares the limitations of the published literature. Given the large volume of randomized trial evidence available from the published literature, we did not make an attempt to contact study authors and obtain individual patient-level information. An individual patient-level data meta-analysis such as that produced by the Cholesterol Treatment Trialists’ Collaboration may provide a more nuanced examination of the comparative effects of statins in specific subgroups – such as those with or without established cardiovascular disease, different age groups, and diabetes status. Third, as a network meta-analysis combining direct and indirect sources of evidence, it remains a possibility that potential imbalances in the occurrence of effect



**Figure 7.** Dose-comparative effects of statins on serum lipid levels according to meta-regression analyses.

Values are mean (95% credible interval). Estimates shown are mean changes from baseline in serum lipid concentrations as compared to control treatment, as adjusted in meta-regression analyses. Findings are shown separately for meta-regressions adjusting for baseline age (A), proportion of women (B), and baseline mean LDL-C concentration (C).

modifiers across the contrasts impacted the results, potentially confounding the comparative estimates between statins. However, this is unlikely given the large body of evidence that provided consistent estimates from a broadly representative group of individuals with different characteristics across trials.

Given the Bayesian nature of the analysis, we did not quantify the extent of potential heterogeneity using the commonly used  $I^2$  statistic. Instead, we directly quantified the between-study heterogeneity, which was found to be low. In addition, we made every attempt to visually inspect potential discrepancies in the reported results across trials. We assessed the consistency of direct and mixed findings in the analysis by comparing

the 95% CI of estimates obtained from analyses including only direct (head-to-head) trials and from those that combined direct trials with placebo-controlled trials. We also performed meta-regression analyses to evaluate whether potential heterogeneity or inconsistency could be explained by baseline LDL-C levels across trials. This statistical exploration did not find evidence that baseline LDL-C had an impact on the relative treatment effects.

This review has important strengths. Based on 256,827 individuals in 181 randomized controlled trials, this network meta-analysis provides the most comprehensive evidence on the relative potency of individual statins in reducing LDL-C and Total-C, and increasing HDL-C. We included evidence from both

**Table 2.** Statistically equivalent doses of statins and expected LDL-C changes

Statin dose (per day)	Target reduction	Estimated LDL-C reduction from pretreatment levels
Atorva >40 mg Rosuva >10 mg Simva >40 mg	High	Prescribers can expect an approximately 45% reduction from pretreatment LDL-C levels with 95% of reductions ranging from 23% to 66% Evidence is most consistent for atorvastatin. This agent should be preferred to initiate therapy
Atorva ≤40 mg Fluva >40 mg Lova >20 mg Prava >20 mg Rosuva ≤10 mg Simva >10 and ≤40 mg	Medium	Prescribers can expect an approximately 38% reduction from pretreatment LDL-C levels with 95% of reductions ranging between 6% and 61% The uncertainty is due in large part to the variability in the evidence base for fluvastatin and pravastatin (at their highest doses) Evidence is most consistent for atorvastatin, rosuvastatin, and simvastatin. These agents should be preferred to initiate therapy
Fluva ≤40 mg Lova ≤20 mg Prava ≤20 mg Simva ≤20 mg	Low	Prescribers can expect an approximately 20% reduction from pretreatment LDL-C levels. In 95% of the cases, patients are estimated to experience changes between 10% increase* and 42% decrease in their baseline LDL-C concentrations  *Lowest doses of fluvastatin and lovastatin may at times not result in reductions in baseline LDL-C levels Evidence is most consistent for pravastatin and simvastatin. These agents should be preferred to initiate therapy

placebo-controlled and active-comparator trials, considerably broadening the evidence base considered in previous reviews. To the best of our knowledge, ours is the first network meta-analysis that included more direct head-to-head trials than placebo-controlled trials, considerably strengthening the statistical inferences of our findings. Including titration design trials considerably improved the generalizability of our findings as titration better reflects common practice in cholesterol management. As a result of our inclusive approach, our findings are generalizable to individuals in clinical practice. We included a broad range of patients and observed that the cholesterol-lowering effects of statins are consistent in studies with populations that varied in age, geographic region, and severity of underlying illness, which adds to the strength of our overall inferences. The findings of the meta-regression analyses provide supportive evidence to suggest that the LDL-lowering effects of individual statins do not differ by differences across the literature in age, sex, baseline LDL-C concentration, and existing coronary heart disease.

In conclusion, this report is the most comprehensive meta-analysis of the effect of statins on reductions in serum lipids, and one of the first to integrate direct head-to-head comparisons between statins. Most interestingly we report the findings of our multiple-treatments meta-analysis on the effect of different statins on serum LDL-C, Total-C, and HDL-C levels. Overall, high-dose statins were associated with greater reductions in pretreatment LDL-C and Total-C concentrations as compared to low-dose regimens

confirming a dose–response relationship. When individual statins were compared head-to-head, several statins appeared to outperform other statins in reducing serum LDL-C and Total-C concentrations. In our meta-analysis, atorvastatin, rosuvastatin, and simvastatin ranked first in terms of reducing serum LDL-C and Total-C as compared to the other statins in the analysis. The LDL-C-reducing effects of some statins appear less pronounced than the findings of previous meta-analyses. Surprisingly, in terms of increasing HDL-C, all statins have only a modest effect on HDL irrespective of dose. The statin prescribing reference table developed in this study will help those in clinical practice to make evidence-based decisions about initiating statin therapy.

### Disclosure statement

Dr Rachael Fleurence currently works for the Patient Centered Outcomes Research Institute. The views expressed in this article do not necessarily represent those of the Patient Centered Outcomes Research Institute.

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# Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials

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## Abstract

**Background:** The extent to which individual statins vary in terms of clinical outcomes across all populations, in addition to secondary and primary prevention has not been studied extensively in meta-analyses.

**Methods:** We systematically studied 199,721 participants in 92 placebo-controlled and active-comparator trials comparing atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin in participants with, or at risk of developing, cardiovascular disease. We performed pairwise and network meta-analyses for major coronary events and all-cause mortality outcomes, taking into account the dose differences across trials. Systematic review registration: PROSPERO 2011:CRD42011001470.

**Results:** There were only a few trials that evaluated fluvastatin. Most frequent comparisons occurred between pravastatin and placebo, atorvastatin and placebo, and rosuvastatin and atorvastatin. No trial directly compared all six statins to each other. Across all populations, statins were significantly more effective than control in reducing all-cause mortality (OR 0.87, 95% credible interval 0.82–0.92) and major coronary events (OR 0.69, 95% CI 0.64–0.75). In terms of reducing major coronary events, atorvastatin (OR 0.66, 95% CI 0.48–0.94) and fluvastatin (OR 0.59, 95% CI 0.36–0.95) were significantly more effective than rosuvastatin at comparable doses. In participants with cardiovascular disease, statins significantly reduced deaths (OR 0.82, 95% CI 0.75–0.90) and major coronary events (OR 0.69, 95% CI 0.62–0.77). Atorvastatin was significantly more effective than pravastatin (OR 0.65, 95% CI 0.43–0.99) and simvastatin (OR 0.68, 95% CI 0.38–0.98) for secondary prevention of major coronary events. In primary prevention, statins significantly reduced deaths (OR 0.91, 95% CI 0.83–0.99) and major coronary events (OR 0.69, 95% CI 0.61–0.79) with no differences among individual statins. Across all populations, atorvastatin (80%), fluvastatin (79%), and simvastatin (62%) had the highest overall probability of being the best treatment in terms of both outcomes. Higher doses of atorvastatin and fluvastatin had the highest number of significant differences in preventing major coronary events compared with other statins. No significant heterogeneity or inconsistency was detected.

**Conclusions:** Statins significantly reduce the incidence of all-cause mortality and major coronary events as compared to control in both secondary and primary prevention. This analysis provides evidence for potential differences between individual statins, which are not fully explained by their low-density lipoprotein cholesterol-reducing effects. The observed differences between statins should be investigated in future prospective studies.

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Meta-analysis, mixed treatment comparison, prevention of coronary heart disease, statins, systematic review

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## Introduction

Statins are widely used to prolong survival and reduce the occurrence of coronary and cerebrovascular events in patients with cardiovascular disease. Prior meta-analyses have demonstrated the effectiveness of statins in secondary prevention,<sup>1–10</sup> among the elderly,<sup>11,12</sup> and in individuals with diabetes.<sup>13,14</sup> Initially focused on secondary prevention, statin therapy has become more common as the limits of treatment have expanded over time to include persons at progressively lower risk of developing cardiovascular disease.<sup>15</sup> As the number of individuals eligible for statin therapy continues to increase both in primary and secondary prevention, two questions warrant further investigation. First, there is no consensus around the benefit of statins in primary prevention.<sup>16</sup> Although previous meta-analyses have provided evidence in support of the use of statins in individuals with no evidence of cardiovascular disease,<sup>17</sup> recent studies challenged these findings.<sup>18,19</sup> Second, whether individual statins vary in terms of their effect on clinical outcomes when compared head-to-head is unclear and has not been studied in a comprehensive manner in previous meta-analyses.<sup>20</sup> Information regarding the relative clinical value of different statins in primary and secondary prevention of cardiovascular disease is needed to better inform patients, clinicians, and other healthcare decision makers.

Previous network meta-analyses that indirectly compared individual statins were limited to placebo-controlled trials and did not take into account evidence from a large number of active-comparator trials.<sup>21–23</sup> Equally importantly, these analyses did not differentiate between primary- and secondary-prevention populations.<sup>24</sup> Finally, previous network meta-analyses did not assess differences in dosages of individual statins across populations and did not compare statins at similar doses.

We report a comprehensive network meta-analysis that combines evidence from both placebo-controlled and active-comparator trials. We evaluate the effect of statins on major coronary events and all-cause mortality across all populations, in addition to secondary and primary prevention of cardiovascular disease separately. We also compare the effectiveness of different statins head-to-head in these patient populations,

taking into account dose differences across the included set of trials.

## Methods

### Study protocol

We developed a protocol and subsequently made it publicly available on the first author's institutional website before starting this study (PROSPERO registration: 2011:CRD42011001470).<sup>25</sup>

### Search strategy and selection criteria

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials to identify studies published between 1 January 1985 and 1 January 2011. To identify the active-comparator trials that were not included in previous meta-analyses, we developed a search strategy using the search terms atorvastatin, fluvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, cholesterol, cardiovascular disease, and hydroxymethylglutaryl-CoA reductase inhibitors/therapeutic use. We also performed manual searches using the authors' files and reference lists from original communications and review articles to cross check references. Two researchers (BT, HT) independently performed abstract, title, and full-text screening. A third researcher approved study selection (HN).

We included open-label and double-blind randomized controlled trials comparing one statin with another at any dose or with control (placebo, diet, or usual care) for adults with, or at risk of developing, cardiovascular disease. We included trials of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin if they had more than 50 participants per trial arm, lasted longer than 4 weeks, and reported major coronary events or all-cause mortality. Both fixed-dose and titration designs were included. Per pre-defined criteria, we excluded trials conducted in patients with renal insufficiency.

### Trial categorization

Whenever possible, we categorized included trials as primary prevention, secondary prevention, or mixed

patient population. Trials that included at least 80% of participants without established cardiovascular disease or reported data separately on a sole primary prevention group were categorized as primary prevention. Trials that included at least 80% of participants with established cardiovascular disease or reported data separately on a sole secondary prevention group were categorized as secondary prevention. All remaining trials were categorized as having a mixed patient population.

Whenever possible, we used data extracted in previous meta-analyses to benefit from earlier attempts at contacting authors of trials and obtaining unpublished information. For instance, for the analysis of the primary prevention trials, data inputs used in the recent meta-analysis by Ray et al.<sup>18</sup> were used to ensure that only patients without coronary artery disease at baseline were included.

## Outcomes

Primary outcomes were major coronary events and all-cause mortality. We defined the composite of major coronary events as deaths from coronary heart disease and non-fatal myocardial infarctions.

## Data extraction

We used a structured form to extract data on trial and patient population characteristics, and outcomes. Full list of data extraction elements can be found on our publicly available protocol. We also extracted information on study quality using the Cochrane risk-of-bias tool. One researcher extracted data (HN) and another independently checked for accuracy (BT).

## Statistical analysis

We first qualitatively summarized included trials, describing the types of direct and indirect comparisons and important clinical and methodological variables (such as trial population, year of publication, age, and risk of cardiovascular disease).

For each pairwise comparison between two treatments, we calculated the relative effect with a 95% confidence interval. First, we performed classical pairwise meta-analyses to synthesize studies that compared the same two treatments using the Mantel-Haenszel (fixed-effect) and Der Simonian Laird (random-effects) method.<sup>26</sup> Forest plots of the relative treatment effects from the individual trials and pairwise meta-analyses were visually inspected to search for heterogeneity. We also statistically inspected heterogeneity using the  $I^2$  measure.

To determine the comparative effects of statins, we conducted network meta-analyses.<sup>27</sup> This type of

analysis allowed for combining the direct within-trial comparisons between two treatments (atorvastatin vs. control) with indirect comparisons constructed from trials that had one treatment in common (atorvastatin vs. control and simvastatin vs. control).<sup>28</sup> This analysis preserved the within-trial randomized treatment comparison of each trial while combining all available comparisons between treatments. Study-level relative treatment effects were combined using random-effects models using Bayesian Markov chain Monte Carlo methods.<sup>29</sup> We considered the findings significant when the 95% credible intervals (CI) for odds ratios (OR) did not include the null value 1.00. We assessed the probability that each statin is best by calculating its treatment effect compared with control and counting the proportion of iterations of the Markov chain in which each statin has the highest treatment effect, the second highest, and so on. This approach took into account the magnitude of the estimated odds ratio as well as the uncertainty around it. We developed rankograms and cumulative probability plots to graphically present the distribution of ranking probabilities and estimated the surface under the cumulative ranking (SUCRA) line for each statin.<sup>30</sup> To estimate inconsistency between direct and indirect evidence, we calculated the ratio of relative effects for indirect vs. direct evidence. We defined inconsistency as the disagreement between direct and indirect evidence with a 95% CI excluding 1.<sup>31</sup>

To obtain a comprehensive estimate of the effect of statins in major coronary events and all-cause mortality, our network meta-analysis pooled all primary and secondary prevention trials in addition to trials with mixed patient populations, including all placebo-controlled and active-comparator trials eligible for inclusion in this review. We also performed separate analyses for the primary and secondary prevention populations, as categorized by the criteria mentioned above.

For the base-case analysis, we excluded trials with high doses (80 mg/day for atorvastatin, fluvastatin, lovastatin, simvastatin, and  $\geq 40$  mg/day for rosuvastatin) and evaluated the benefits of statins at comparable doses. In a sensitivity analysis, we also included trials that evaluated statins at high doses. A dose-specific analysis explored the effects of individual statins at low, medium, and high doses separately. We categorized doses as low ( $\leq 20$  mg/day), medium (21–40 mg/day), and high ( $> 40$  mg/day) for atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. For rosuvastatin, doses  $\leq 10$  mg/day was categorized as low, 11–20 mg/day as medium, and  $> 20$  mg/day as high.

We also investigated whether potential heterogeneity and inconsistency across the evidence base in the

network meta-analysis could be explained by differences in study-level covariates. We performed meta-regression analyses to evaluate whether differences in trial publication year, patients' baseline LDL concentration, and age could explain potential heterogeneity. We performed all meta-regression analyses by allowing for a common treatment-covariate interaction for each statin compared to control.<sup>32</sup>

All analyses were based on the total number of randomly assigned participants. We conducted pairwise meta-analyses in STATA 11.0, multiple-treatments meta-analyses in WinBugs 1.4.3, and evaluated inconsistency in the trial network using R 2.11.1. Graphical presentation of the trial network, inconsistency plots, rankograms, and SUCRA plots were developed in R 2.11.1.

## Results

We included 92 trials (Figure 1), totalling 199,721 participants (Supplemental Table S1). Overall, the average trial duration was 116 weeks (2.2 years). There were 59 two-armed placebo-controlled trials and the remaining 33 were two- or multi-armed active-comparator trials. Of the 15 possible pairwise comparisons between the six statins, nine were available for the all-cause mortality outcome and only six were available for the major coronary events outcome. There were only a few trials that evaluated fluvastatin. Most frequent comparisons occurred between pravastatin and placebo, atorvastatin and placebo, and rosuvastatin and atorvastatin. There were 4709 participants in the placebo-controlled trials of fluvastatin as compared to 54,617 and 28,762 in the placebo-controlled trials of pravastatin and rosuvastatin, respectively. No trial directly compared all six statins with each other (Figure 2).

The overall quality of included trials was rated as moderate. Older trials were more prone to bias with inadequate sequence generation and treatment allocation concealment. A large number of trials did not report details about randomization procedures and allocation concealment. Only a small number of trials were at low risk of bias.

### *Pairwise meta-analysis findings: benefit of statin therapy vs. control*

In the pairwise meta-analysis of statin therapy vs. control, 157,217 participants contributed information on 12,398 deaths, and 153,578 participants contributed information on 9715 major coronary events. Overall, statin therapy was associated with a reduction in all-cause mortality (OR 0.87, 95% CI 0.82–0.92) (Figure 3) and major coronary events (OR 0.69, 95% CI 0.64–0.75) when compared to control (Figure 4). Among

statins, only fluvastatin and pravastatin were associated with a significant reduction in all-cause mortality compared with the control, while atorvastatin, lovastatin, rosuvastatin, and simvastatin were not. Atorvastatin, fluvastatin, pravastatin, and simvastatin were associated with significantly fewer major coronary events than control treatment.

In the secondary prevention population, statin therapy was associated with a significant reduction in all-cause mortality (OR 0.82, 95% CI 0.75–0.90) and major coronary events (OR 0.69, 95% CI 0.62–0.77) when compared to control. Fluvastatin and pravastatin resulted in significantly fewer deaths as compared to control (Figure 3), while atorvastatin, fluvastatin, and pravastatin led to significantly fewer major coronary events than control treatment (Figure 4).

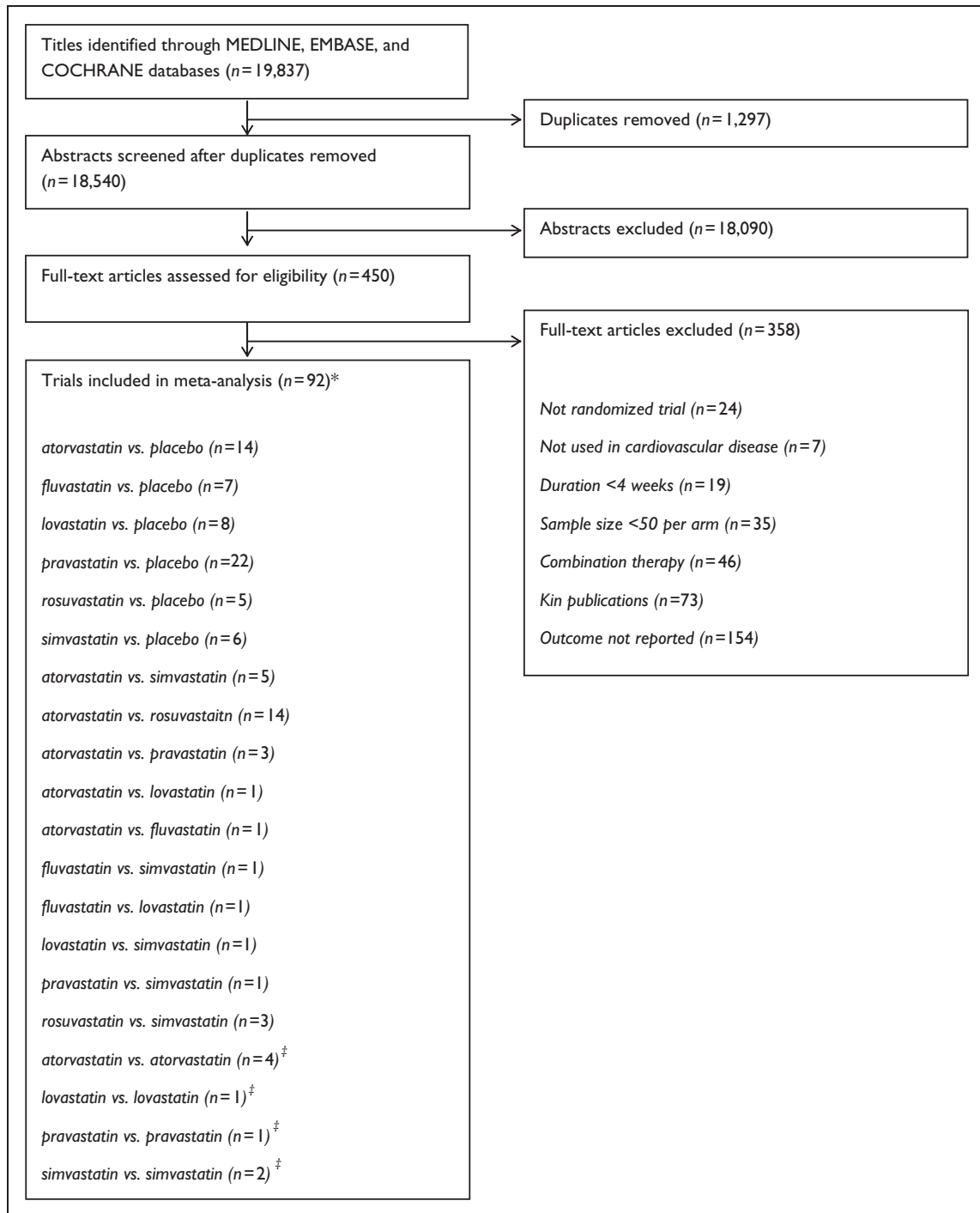
In the primary prevention population, statin therapy was associated with a significant reduction in all-cause mortality (OR 0.91, 95% CI 0.83–0.99) (Figure 3) and major coronary events (OR 0.69, 95% CI 0.61–0.79) (Figure 4). In this population, only rosuvastatin had sufficient evidence for a significant benefit on all-cause mortality, while atorvastatin, fluvastatin, lovastatin, and pravastatin did not. Atorvastatin, lovastatin, pravastatin, and rosuvastatin were associated with significantly fewer major coronary events as compared to control.

Overall, statistical heterogeneity in pairwise comparisons of statin therapy vs. control in all-cause mortality was low to moderate in analyses of primary prevention ( $I^2$  8.9%), secondary prevention ( $I^2$  14.8%), and all populations together ( $I^2$  22.6%). We observed moderate heterogeneity in pairwise comparisons of statin therapy vs. control in major coronary events ( $I^2$  29.4% in secondary prevention,  $I^2$  40.2% in primary prevention, and  $I^2$  40.9% in all populations together).

### *Network meta-analysis findings: comparative benefits of statins*

In addition to the trials included in the pairwise comparisons of statin therapy vs. control, there were 39 direct head-to-head statin comparisons, providing information on 43,174 participants. In the base-case network meta-analysis, 64 and 48 trials provided information for the all-cause mortality and major coronary events analyses, respectively. In total, 161,379 participants were included in the base-case analysis on all-cause mortality, which provided information on 11,914 deaths. For the major coronary events outcome, there were 9363 events among 151,520 participants.

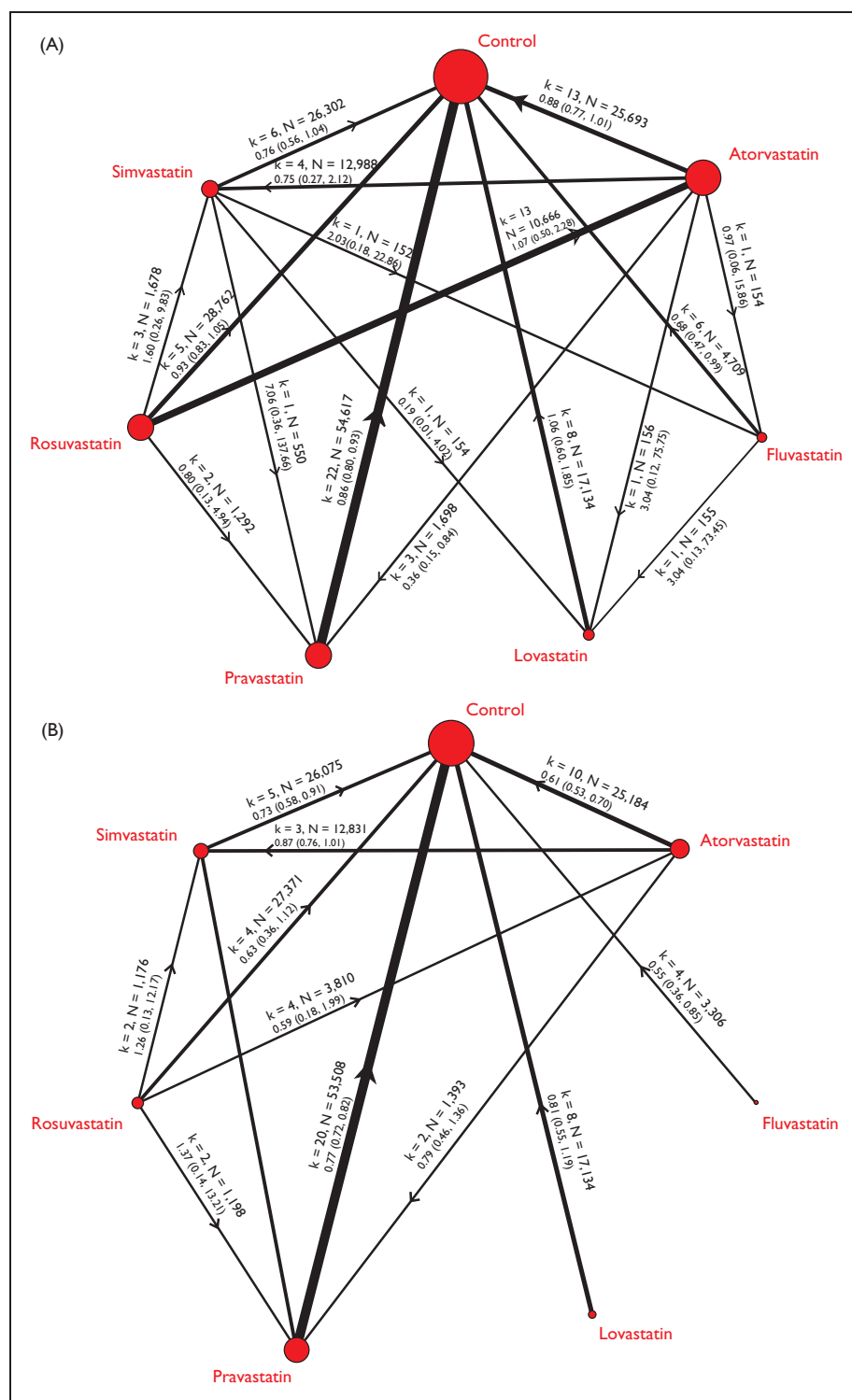
In the sensitivity analysis inclusive of high-dose trials, 80 and 62 trials provided information for the all-cause mortality and major coronary events analyses,



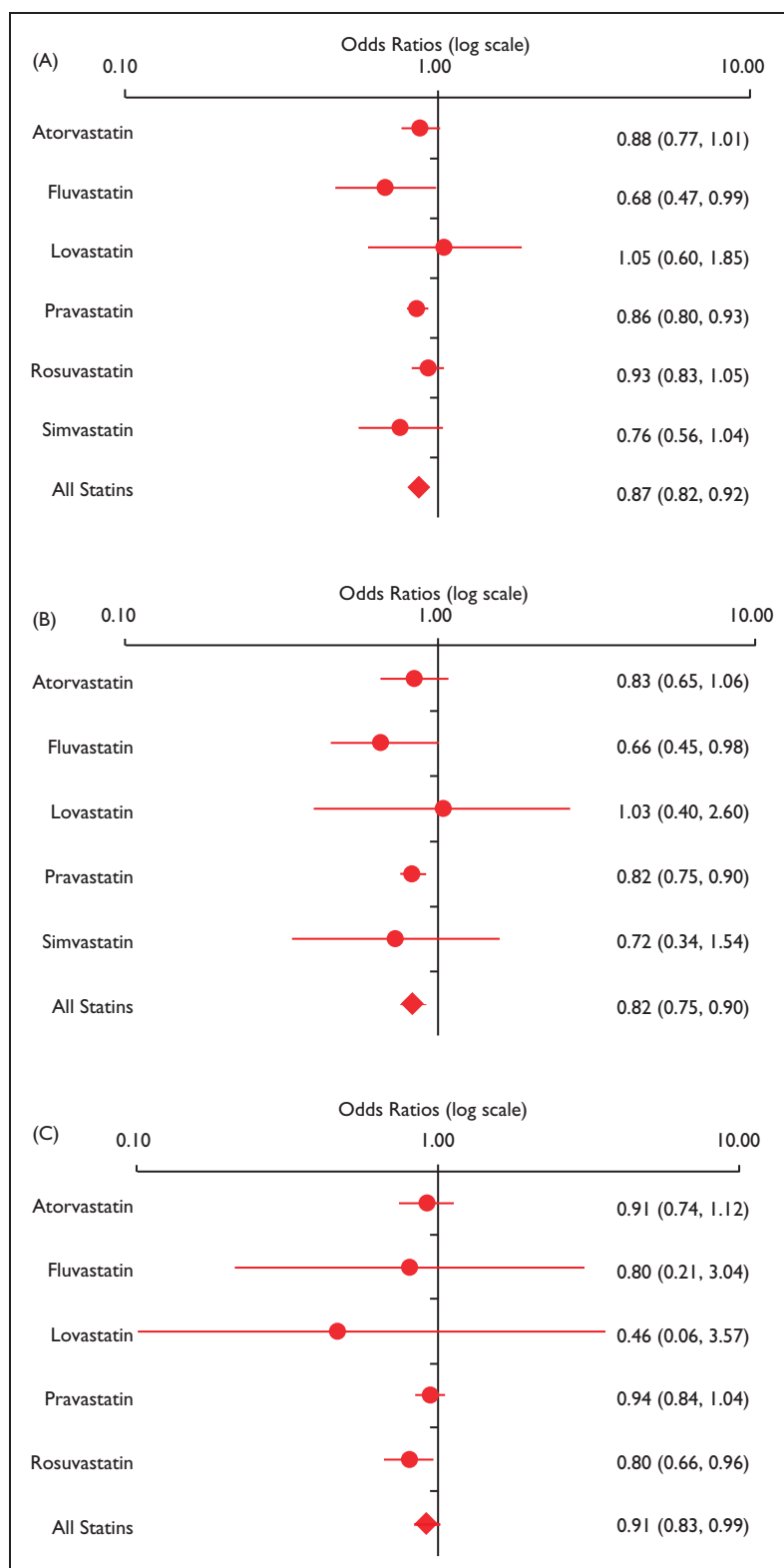
**Figure 1.** Flow diagram of trial identification and selection.

\*Ninety-two randomized trials correspond to 101 comparisons because some trials had more than two arms.

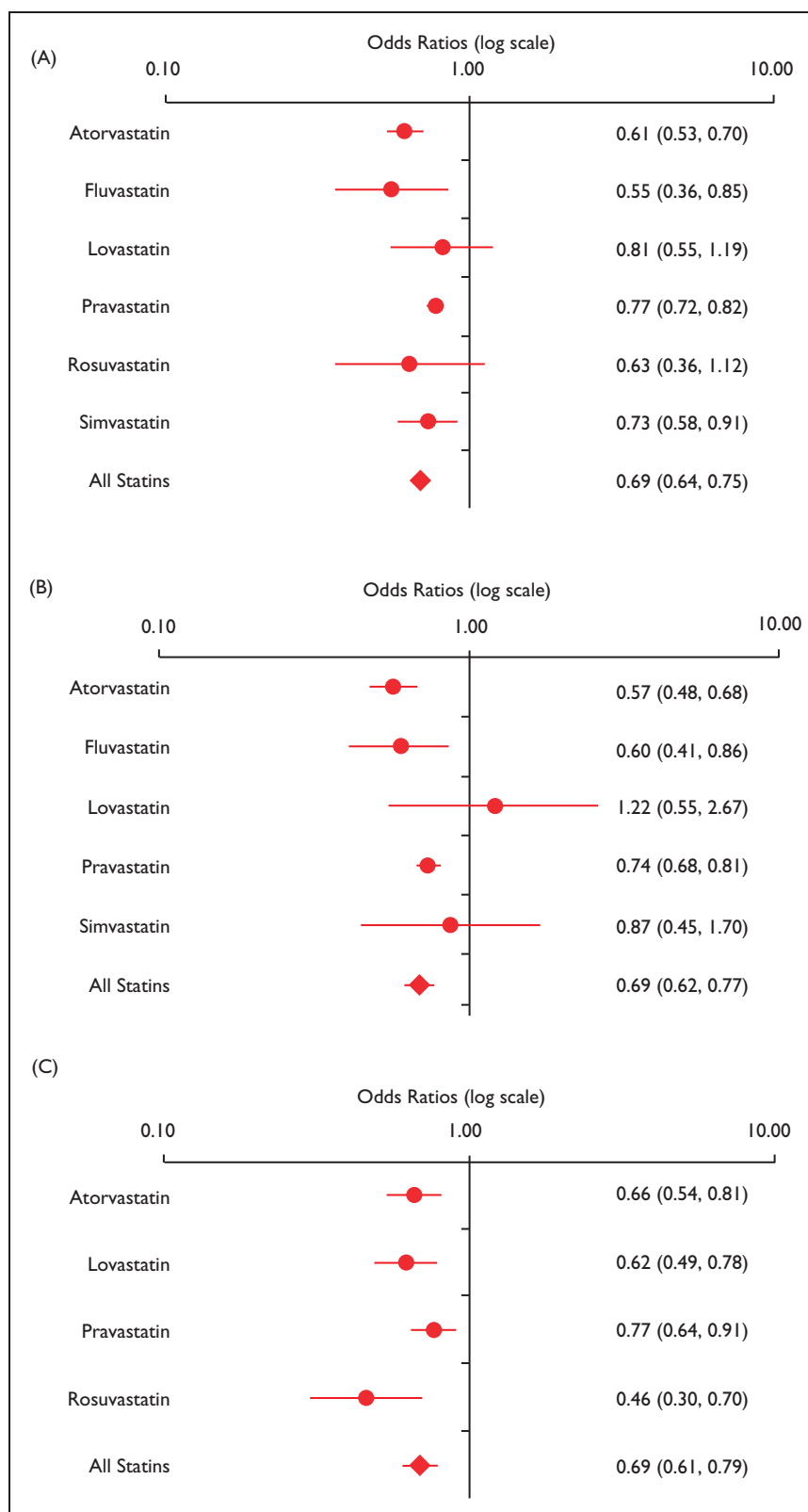
‡Eight randomized trials compared the same statin at a high dose vs. low dose.



**Figure 2.** Network of eligible pairwise comparisons for (A) all-cause mortality and (B) major coronary events in placebo-controlled and active-comparator trials of participants with and without prior coronary heart disease at baseline (overall population). Connecting lines indicate the direct pairwise comparison between two treatments ( $k$  = number of pairwise comparisons;  $N$  = overall number of participants; odds ratios and 95% confidence intervals are given). Arrows depict the direction of comparison (e.g. atorvastatin vs. control). Supplementary Figures S1 (all-cause mortality) and S2 (major coronary events) provide separate network diagrams for secondary and primary prevention populations. A total of 93 out of 101 comparisons are shown in these network diagrams as eight trials compared the same statin (high vs. low dose comparisons), which are not depicted in this figure.



**Figure 3.** Findings of pairwise meta-analyses: effect of statins compared to control on all-cause mortality in placebo-controlled trials of participants (A) with and without prior coronary heart disease at baseline (overall population), (B) with coronary heart disease at baseline (secondary prevention), (C) without coronary heart disease at baseline (primary prevention). Results shown are based on an analysis of 157,217 participants in placebo-controlled trials. Supplementary Figures S3 (overall population), S4 (secondary prevention), and S5 (primary prevention) provide the list of studies and their findings included in separate meta-analyses.



**Figure 4.** Findings of pairwise meta-analyses: effect of statins compared to control on major coronary events in placebo-controlled trials of participants (A) with and without prior coronary heart disease at baseline (overall population), (B) with coronary heart disease at baseline (secondary prevention), (C) without coronary heart disease at baseline (primary prevention). Results shown are based on an analysis of 153,578 participants. Supplementary Figures S6 (overall population), S7 (secondary prevention), and S8 (primary prevention) provide the list of studies and their findings included in separate meta-analyses.

respectively. In total, 183,844 participants were included in the sensitivity analysis on all-cause mortality, which provided information on a total of 13,210 deaths. For the major coronary events outcome, there were 10,664 events among 173,062 participants.

In the dose-specific analysis that included all placebo-controlled, active-comparator, and dose-comparison trials, a total of 13,892 deaths among 196,765 participants in 86 trials, and 11,515 major coronary events among 186,375 participants in 69 trials, were included.

In the base-case analysis, the average dose was 16.7 mg/day for atorvastatin as compared to 40.0 mg/day for fluvastatin, 39.3 mg/day for lovastatin, 30.9 mg/day for pravastatin, 14.8 mg/day for rosuvastatin, and 33.3 mg/day for simvastatin. In this analysis, there were no significant differences among statins in terms of all-cause mortality when all trials of primary prevention, secondary prevention, and mixed patient populations were pooled (Figure 5). For the overall population, rosuvastatin resulted in significantly fewer major coronary events compared to atorvastatin and fluvastatin. Among participants with established cardiovascular disease, atorvastatin was associated with significantly fewer major coronary events compared to pravastatin and simvastatin. There were no statistical differences among individual statins without established cardiovascular disease.

In the sensitivity analysis, the average dose of atorvastatin was 39.6 mg/day as compared to 72.3 mg/day for fluvastatin, 40.7 mg/day for lovastatin, 31.2 mg/day for pravastatin, 17.2 mg/day for rosuvastatin, and 33.3 mg/day for simvastatin. There were no significant differences in the treatment benefit among statins when we pooled trials of primary prevention, secondary prevention, and mixed patient populations for both all-cause mortality and major coronary events (Figure 6). However, among participants with established cardiovascular disease, atorvastatin was associated with significantly fewer major coronary events compared to pravastatin. Participants randomized to lovastatin were estimated to experience significantly more major coronary events than those randomized to atorvastatin, fluvastatin, and simvastatin in trials of secondary prevention. There were no detectable statistical differences among statins for participants without established cardiovascular disease.

When we ranked statins according to cumulative probability of reducing all-cause mortality and major coronary events across all populations, atorvastatin (80%), fluvastatin (79%), and simvastatin (62%) were among the most effective treatments at comparable doses (Figure 7). In a sensitivity analysis, fluvastatin (89%), atorvastatin (76%), and simvastatin (60%) consistently ranked as the most effective treatments when high-dose trials were included in the analysis.

In the dose-specific analysis, low-dose atorvastatin and low-dose pravastatin resulted in significantly fewer deaths than control treatment while other statins did not have adequate evidence to show superiority over placebo (Figure 8). Statins in higher doses did not have a greater impact on all-cause mortality than lower doses. In terms of major coronary events, all statins except for low-dose lovastatin, high-dose lovastatin, low-dose rosuvastatin, high-dose rosuvastatin, and low-dose simvastatin were associated with significantly fewer major coronary events as compared to control treatment. Higher doses of atorvastatin and fluvastatin had the highest number of significant differences compared with other statins (Supplementary Figure S13).

There was no evidence of inconsistency in the trial network as the direct estimate of the summary effect did not differentiate from the indirect estimate in each loop of the network for both outcomes (Supplementary Figures S14 and 15). Comparative benefit estimates of statins did not change in meta-regression analyses when we adjusted for publication year and baseline mean age of patients. Although we detected a modest association between mean LDL concentrations of patients at baseline and effects of statins, comparative effect estimates did not change after adjustment (Supplementary Exhibit S1).

## Discussion

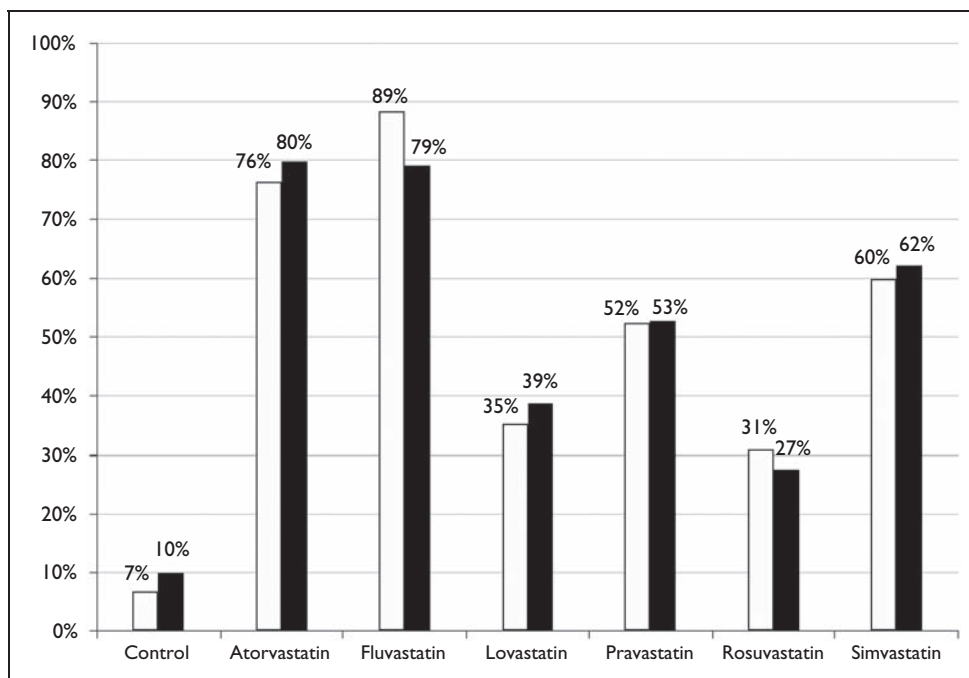
This network meta-analysis of 199,721 participants provides evidence on the statistically and clinically meaningful benefits of statins in both primary and secondary prevention of all-cause mortality and major coronary events. Overall, statins were associated with an 18% reduction in relative odds of all-cause mortality among patients with cardiovascular disease. In primary prevention, statin therapy resulted in a modest but significant 9% reduction in relative odds of all-cause mortality. Benefits of statins in reducing the relative odds of major coronary events by 31% were consistent across primary and secondary prevention populations. This meta-analysis is the most comprehensive study to investigate the comparative effect of different statins using both placebo-controlled and active-comparator trials and separately for primary- and secondary-prevention populations. Existing statin trial evidence appeared asymmetric given the extremely small numbers of individuals included in fluvastatin trials relative to other statins. Across all populations, our base-case analysis provided evidence to suggest that there may be differences among individual statins for preventing coronary events. Among statins, atorvastatin, fluvastatin, and simvastatin were likely to be ranked superior to their alternatives at comparable doses across all populations.

(A)					
Atorvastatin	1.11 (0.42, 2.79)	0.78 (0.52, 1.14)	0.91 (0.72, 1.11)	0.85 (0.64, 1.07)	0.99 (0.73, 1.28)
1.13 (0.70, 1.85)	Fluvastatin	0.71 (0.26, 1.87)	0.82 (0.33, 2.13)	0.76 (0.30, 2.00)	0.89 (0.34, 2.32)
0.83 (0.57, 1.16)	0.74 (0.42, 1.20)	Lovastatin	1.16 (0.80, 1.68)	1.08 (0.73, 1.61)	1.26 (0.84, 1.89)
0.82 (0.65, 1.11)	0.73 (0.48, 1.16)	0.99 (0.74, 1.47)	Pravastatin	0.93 (0.75, 1.17)	1.08 (0.85, 1.39)
<b>0.66</b> <b>(0.48, 0.94)</b>	<b>0.59</b> <b>(0.36, 0.95)</b>	0.79 (0.56, 1.22)	0.81 (0.58, 1.04)	Rosuvastatin	1.16 (0.88, 1.53)
0.83 (0.58, 1.10)	0.74 (0.43, 1.15)	1.00 (0.69, 1.38)	1.02 (0.68, 1.24)	1.27 (0.82, 1.67)	Simvastatin
(B)					
Atorvastatin	1.02 (0.20, 5.00)	0.93 (0.20, 4.13)	0.65 (0.24, 1.22)	0.70 (0.08, 4.18)	0.68 (0.24, 1.43)
—	Fluvastatin	0.92 (0.13, 6.56)	0.62 (0.12, 2.62)	0.67 (0.05, 7.52)	0.66 (0.13, 2.74)
0.65 (0.26, 1.77)	—	Lovastatin	0.68 (0.16, 2.56)	0.72 (0.06, 7.99)	0.72 (0.16, 2.90)
<b>0.65</b> <b>(0.43, 0.99)</b>	—	—	Pravastatin	1.09 (0.12, 8.42)	1.06 (0.52, 2.15)
—	—	—	—	Rosuvastatin	0.97 (0.12, 9.24)
<b>0.68</b> <b>(0.38, 0.98)</b>	—	1.02 (0.36, 2.60)	1.05 (0.61, 1.39)	—	Simvastatin
(C)					
Atorvastatin	0.99 (0.18, 5.43)	0.96 (0.45, 3.47)	0.97 (0.49, 2.17)	0.98 (0.32, 2.47)	—
—	Fluvastatin	1.01 (0.19, 6.68)	1.00 (0.19, 5.21)	0.98 (0.15, 5.53)	—
1.05 (0.51, 2.27)	—	Lovastatin	1.01 (0.34, 2.00)	1.02 (0.22, 2.32)	—
0.90 (0.54, 1.84)	—	0.86 (0.48, 1.81)	Pravastatin	1.02 (0.34, 2.17)	—
1.41 (0.59, 3.45)	—	1.35 (0.52, 3.33)	1.55 (0.63, 3.24)	Rosuvastatin	—
—	—	—	—	—	Simvastatin

**Figure 5.** Base-case analysis findings: comparative effect of individual statins on all-cause mortality (in white) and major coronary events (in grey) according to network meta-analysis of participants (A) with and without coronary heart disease at baseline (overall population), (B) with coronary heart disease at baseline (secondary prevention), and (C) without coronary heart disease at baseline (primary prevention). Values are odds ratios (95% CI). Comparisons between drugs should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, odds ratios less than 1 favour the column-defining treatment. To obtain odds ratios for comparisons in the opposite direction, reciprocals should be taken.

(A)					
Atorvastatin	1.22 (0.80, 1.86)	0.82 (0.57, 1.16)	0.95 (0.78, 1.13)	0.91 (0.73, 1.10)	1.01 (0.73, 1.10)
1.11 (0.72, 1.80)	Fluvastatin	0.66 (0.40, 1.13)	0.77 (0.51, 1.18)	0.74 (0.48, 1.15)	0.82 (0.53, 1.27)
0.83 (0.58, 1.11)	0.74 (0.42, 1.20)	Lovastatin	1.16 (0.81, 1.65)	1.11 (0.77, 1.60)	1.23 (0.85, 1.80)
0.84 (0.70, 1.05)	0.76 (0.48, 1.18)	1.02 (0.77, 1.48)	Pravastatin	0.96 (0.78, 1.17)	1.06 (0.86, 1.32)
0.75 (0.57, 1.02)	0.67 (0.41, 1.09)	0.90 (0.65, 1.40)	0.89 (0.68, 1.17)	Rosuvastatin	1.11 (0.88, 1.40)
0.84 (0.64, 1.01)	0.75 (0.44, 1.17)	1.01 (0.73, 1.41)	1.00 (0.73, 1.22)	1.12 (0.76, 1.47)	Simvastatin
(B)					
Atorvastatin	1.20 (0.72, 1.99)	0.97 (0.42, 2.25)	0.90 (0.66, 1.15)	0.49 (0.12, 1.56)	0.98 (0.68, 1.26)
0.97 (0.67, 1.52)	Fluvastatin	0.82 (0.33, 2.07)	0.75 (0.44, 1.23)	0.41 (0.09, 1.39)	0.82 (0.47, 1.37)
<b>0.47</b> <b>(0.27, 0.83)</b>	<b>0.48</b> <b>(0.24, 0.94)</b>	Lovastatin	0.92 (0.39, 2.12)	0.51 (0.09, 1.97)	1.00 (0.42, 2.33)
<b>0.77</b> <b>(0.64, 0.95)</b>	0.79 (0.52, 1.17)	1.65 (0.96, 2.90)	Pravastatin	0.55 (0.13, 1.77)	1.09 (0.77, 1.50)
–	–	–	–	Rosuvastatin	1.98 (0.60, 8.40)
0.86 (0.67, 1.01)	0.88 (0.54, 1.29)	<b>1.82</b> <b>(1.01, 3.22)</b>	1.12 (0.83, 1.34)	–	Simvastatin
(C)					
Atorvastatin	1.13 (0.25, 5.41)	1.02 (0.59, 2.33)	1.00 (0.67, 1.60)	1.07 (0.51, 1.87)	–
–	Fluvastatin	0.93 (0.19, 4.72)	0.90 (0.19, 4.01)	0.93 (0.18, 4.34)	–
1.10 (0.65, 1.95)	–	Lovastatin	0.98 (0.46, 1.65)	1.06 (0.35, 1.91)	–
0.88 (0.63, 1.43)	–	0.81 (0.51, 1.38)	Pravastatin	1.08 (0.51, 1.75)	–
1.44 (0.73, 2.83)	–	1.30 (0.61, 2.70)	1.61 (0.80, 2.98)	Rosuvastatin	–
–	–	–	–	–	Simvastatin

**Figure 6.** Sensitivity analysis findings: comparative effect of individual statins on all-cause mortality (in white) and major coronary events (in grey) according to network meta-analysis of participants (A) with and without coronary heart disease at baseline (overall population), (B) with coronary heart disease at baseline (secondary prevention), and (C) without coronary heart disease at baseline (primary prevention). Values are odds ratios (95% CI). Comparisons between drugs should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, odds ratios less than 1 favour the column-defining treatment. To obtain odds ratios for comparisons in the opposite direction, reciprocals should be taken.



**Figure 7.** Overall ranking of statins in placebo-controlled and active-comparator trials of participants with and without prior coronary heart disease at baseline (overall population) by their overall probability to be the best treatment in terms of both reducing the risk of all-cause mortality and major coronary events (black). Sensitivity of the overall ranking to inclusion of high-dose trials is also presented (white). Each statin was scored with points up to a maximum of 50 for all-cause mortality and 50 for major coronary events (overall maximum score 100), with data from rankograms and SUCRA. Supplementary Figures S9–S12 present rankograms and SUCRA.

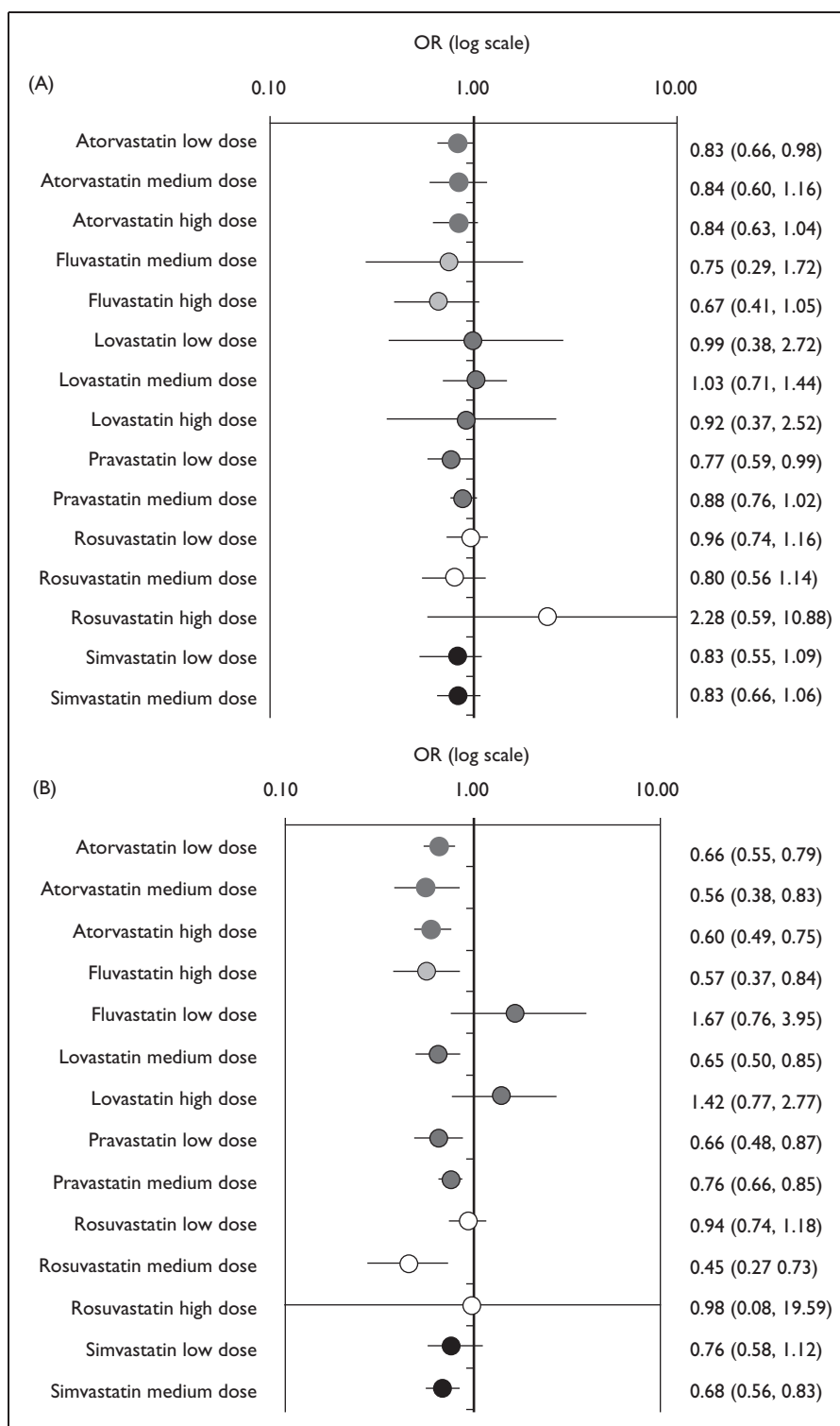
Although the benefits of statins in the secondary prevention setting are well documented,<sup>9</sup> their impact in individuals free of cardiovascular disease has been disputed.<sup>16</sup> The present analysis suggests that all-cause mortality benefits of statins are clinically and statistically significant. With reductions estimated at 9%, our analysis confirms the all-cause mortality benefit of statin therapy observed in previous meta-analyses.<sup>17</sup> In contrast to most recent reviews,<sup>18</sup> our analysis achieved a higher precision around this estimate (with statistical significance) as a result of including trials with very few events that were not considered previously.

Our analysis emphasizes that clinical objectives of primary prevention of cardiovascular disease should not be limited to reductions in all-cause mortality and that decisions about whether to use statins for patients without established cardiovascular disease should include consideration of other outcomes. Our finding that the benefits of statins in preventing major coronary events are consistent across primary and secondary populations provides supporting evidence for prescribing statins to high-risk individuals who stand to benefit from this therapy. This is particularly important as the prevention of coronary events also prevents individuals

from graduating into a considerably higher risk category.

In addition to pairwise meta-analyses that compared statins to control treatment, we also performed network meta-analysis, which is a relatively new method that differs from pairwise meta-analysis by incorporating data from both direct (from head-to-head comparisons within trials) and indirect (from comparisons between trials) sources of evidence. Using this approach, we combined the results of placebo-controlled and active-comparator trials, allowing for more informed estimates of the relative effect of individual statins that have not been compared head-to-head in clinical trials. As with traditional meta-analysis, our network meta-analysis required an assumption of similarity across the pooled set of trials in terms of patient population and trial characteristics. We also assumed consistency in the trial network when we combined both active-comparator and placebo-controlled trials.

Our analysis differed from previous network meta-analyses in three important aspects. First, our review incorporated data from a comprehensive list of trials irrespective of placebo or active controls. Second, we provided comparative estimates separately for primary



**Figure 8.** Dose-specific analysis findings: comparative effect of individual statins compared to control for (A) all-cause mortality and (B) major coronary events in placebo-controlled and active-comparator trials of participants with and without prior coronary heart disease at baseline (overall population).

and secondary prevention populations. Third, we made an attempt to evaluate the comparative efficacy of individual statins at similar doses.

Our base-case analysis detected significant differences among individual statins with potential implications for prescribing decisions in clinical practice. Doses considered in our base-case analysis were comparable and, as expected, resulted in approximately 30–40% reductions from baseline serum low-density lipoprotein cholesterol (LDL-C) levels.<sup>7</sup> Atorvastatin and fluvastatin performed significantly better than rosuvastatin in terms of reducing major coronary events across all populations. Atorvastatin and fluvastatin had a strong effect in reducing mortality and morbidity among individuals with established cardiovascular disease. Among individuals with established disease, atorvastatin resulted in marginally fewer major coronary events as compared with pravastatin and simvastatin. Relative treatment effects for statins were not sensitive to the findings of the meta-regression analysis and the sensitivity analysis that included intensive dose trials. In the sensitivity analysis, atorvastatin was significantly more effective than lovastatin and pravastatin in reducing major coronary events in the secondary prevention setting. Also, fluvastatin was more effective than lovastatin in reducing major coronary events. Unfortunately, fluvastatin and simvastatin had insufficient evidence in the primary prevention setting as there was no trial for either statin that provided information for their effectiveness in high-risk individuals without established disease.

Our dose-specific analysis paralleled the findings of previous meta-analyses in that statins at higher doses do not reduce all-cause mortality more so than statins at lower doses.<sup>33</sup> Similar to previous meta-analyses, there was a general dose-response relationship across placebo-controlled and active-comparator trials in terms of reducing major coronary events. However, this relationship was not apparent for all statins. For instance, low-dose and high-dose formulations of lovastatin fared worse than the medium-dose formulation.<sup>34–37</sup> Similarly, currently available randomized evidence is not adequate to suggest that high-dose rosuvastatin is beneficial in reducing major coronary events.<sup>38–40</sup> Although high-dose formulations of atorvastatin and fluvastatin have not been compared directly in trials, the findings of our network meta-analysis provided compelling evidence that these agents are equally effective in reducing the occurrence of major coronary events. Placebo-controlled trials of atorvastatin and fluvastatin were comparable in terms of known relative treatment effect modifiers and individuals in the placebo arms experienced major coronary events at similar rates.<sup>41–45</sup> Given the greatly differing incremental LDL-C-lowering effects of high-dose atorvastatin

and fluvastatin,<sup>7</sup> this analysis suggests that incremental LDL-C-reducing effects alone may not be responsible for the comparative benefits of statins. In the case of fluvastatin, prospective studies should further evaluate whether pleiotropic effects are responsible for its favourable benefits relative to other statins.<sup>46</sup>

Findings of this study should be interpreted in light of its limitations. First, as a literature-based meta-analysis, our analysis shares the limitations of the published evidence base. The quality of included trials was moderate with older trials being more prone to bias than newer trials. This was particularly the case for the trials of lovastatin and fluvastatin. However, the implications of this in our analysis were not clear. The quality of reporting remains well below an acceptable level, particularly for older trials, which complicates assessments of their conduct and validity.<sup>47</sup> Second, there were only a few head-to-head trials of statins that were prospectively designed to capture differences in clinical outcomes as primary endpoints. Third, there was an apparent asymmetry in the evidence network where specific interventions appear to be avoided (e.g. fluvastatin), which may be indicative of a biased clinical research agenda. The reasons behind this should be investigated further. Fourth, heterogeneity ranged from low to moderate across various pairwise meta-analyses of statins vs. control. Although the estimate of between-study heterogeneity was low in network meta-analyses, it remains a possibility that our analysis did not fully account for heterogeneity due to unobserved or unmeasured factors. However, we used a random-effects model and our analyses took into account potential unexplained heterogeneity across the studies. We also performed meta-regressions to further evaluate heterogeneity and inconsistency and did not detect a significant association between publication year and baseline age of patients. According to meta-regressions, findings of our analysis were consistent with previous reviews that showed that the impact of statins might vary modestly across differing levels of baseline LDL-C.

Heterogeneity that is unexplained or unaccounted for may introduce bias only if it influences different statins to a different extent.<sup>48</sup> For instance, it is possible that there is an imbalance across the included set of trials in terms of baseline characteristics: trials of atorvastatin may have included patients who were on average older than those of pravastatin. Although baseline age is not a relative effect modifier, as shown in previous individual patient-level meta-analyses, there may be imbalances across studies in terms of unmeasured or unknown relative effect modifiers. Hence, we caution, as we would in any meta-analysis, that any comparison of statins should be tempered by the differences that may result from additional (unobserved or

unmeasured) differences in patient populations across different trials. An individual patient-level data meta-analysis such as that produced by the Cholesterol Treatment Trialists' Collaboration<sup>9,49</sup> may provide a more nuanced examination of the comparative benefits of statins in specific subgroups – such as those with or without cardiovascular disease, by age, and diabetes status.

In spite of these limitations, this study has important methodological strengths. Our review is the largest meta-analysis on statin therapy to-date. We included 39 direct head-to-head statin comparisons, providing information on 43,174 participants that were not considered in prior meta-analyses on clinical outcomes. Due to the comprehensive nature of our review, our findings are generalizable to patients in clinical practice. We included a broad range of patients and observed that the benefits of statins are consistent in studies with populations that varied in age, geographic region, and severity of underlying illness, which adds to the strength of our overall inferences – providing conclusive evidence that statins work in both primary and secondary prevention, and that there may be differences between individual statins, which should be investigated in future prospective studies.

What are the clinical implications of this network meta-analysis when initiating statin therapy? First, there is strong evidence that statins as a class are effective in the primary and secondary prevention of major coronary events and all-cause mortality. According to the findings of this comprehensive analysis, there is consistently strong evidence on the benefits of atorvastatin and simvastatin, which should be favoured in clinical practice. Although fluvastatin ranked superior to its alternatives in our analyses, we caution against over-interpreting this finding, particularly given the small number of trials that evaluated this agent. Future studies on fluvastatin are needed to confirm its favourable effect on mortality and coronary disease outcomes. Finally, we acknowledge the multifaceted nature of making prescribing decisions and urge prescribers to also consider other important outcomes such as harmful side effects when choosing among individual statins.

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### Statement

The views expressed in this paper are not necessarily those of Patient Centered Outcomes Research Institute.

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## Review

QJM

**Comparative effects of statins on major cerebrovascular events: a multiple-treatments meta-analysis of placebo-controlled and active-comparator trials**H. NACI<sup>1</sup>, J.J. BRUGTS<sup>2</sup>, R. FLEURENCE<sup>3</sup> and A.E. ADES<sup>4</sup>

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**Summary**

Statins are important in the prevention of major cerebrovascular events. Whether, and the extent to which, individual statins differ in terms of their effect on these outcomes has not been studied. The aim of this review was to evaluate the comparative effects of individual statins on major cerebrovascular events. We systematically reviewed 61 trials including 187 038 individuals with, or at risk of developing, cardiovascular disease. We performed pair-wise and multiple-treatments meta-analyses for major cerebrovascular events, in addition to fatal and non-fatal strokes separately. Across all populations, statins were significantly more effective than control in reducing major cerebrovascular events [odds ratio (OR): 0.82, 95% CI: 0.77, 0.87], with no differences among individual statins. Statins were also effective in patients with established cardiovascular disease (OR: 0.83, 95%

CI: 0.75, 0.91) and in those without (OR: 0.80, 95% CI: 0.71, 0.91). Considering individual statins, significant risk reductions were achieved with atorvastatin (OR: 0.74, 95% CI: 0.63, 0.85), pravastatin (OR: 0.86, 95% CI: 0.76, 0.97) and simvastatin (OR: 0.75, 95% CI: 0.62, 0.88) as compared with control on major cerebrovascular events across all populations. Statins led to significant reductions in the risk of non-fatal strokes (OR: 0.77, 95% CI: 0.71, 0.85) but not of fatal strokes (OR: 0.96, 95% CI: 0.80, 1.15). Findings were not sensitive to dose differentials of individual statins across the trials. No significant heterogeneity or inconsistency was detected. Statins significantly reduce the incidence of major cerebrovascular events as compared with control. Our analysis provided evidence to confirm the class effect of statins in preventing major cerebrovascular events.

**Introduction**

Stroke is among the leading causes of death and disability worldwide. Annually, ~16 million incident strokes occur globally, causing an estimated total of 5.7 million deaths.<sup>1</sup> About half of stroke survivors

experience physical or cognitive impairment, impacting their physical function, social function and activities of daily living.<sup>2</sup> In addition to its health impact, stroke is costly to individuals, their families and the wider society—with an economic burden amounting to an estimated \$65.5 billion in the USA alone.<sup>3,4</sup>

Although the evidence from epidemiological studies remains inconclusive,<sup>5,6</sup> lipid management is an important milestone in the prevention of stroke.<sup>7</sup> Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, also known as statins, effectively reduce the risk of strokes.<sup>8,9</sup> Recent reviews and meta-analyses of randomized controlled trials have confirmed the considerable benefits of statins in the prevention of strokes among individuals with a history of established cardiovascular disease.<sup>10–15</sup> Previous meta-analyses showed that statins effectively reduce the risk of stroke in the elderly,<sup>16,17</sup> among diabetics<sup>18,19</sup> and in individuals with no established cardiovascular disease.<sup>20–22</sup> According to analyses of individual patient-level data from different trials, there appear to be a significant trend towards greater proportional reductions in stroke being associated with greater mean absolute low-density lipoprotein (LDL) cholesterol reductions.<sup>23</sup> Indeed, in direct comparisons of different dosing regimens, high-dose statin therapy reduces the risk of stroke to a greater extent compared with standard doses.<sup>24</sup>

An important question that remains unanswered in previous meta-analyses is whether individual statins are different in terms of their effect on the risk of stroke in individuals with or without a history of established cardiovascular disease. Earlier meta-analyses did not address this question in part because their focus was to establish the class effect of statins over control treatment on the basis of placebo-controlled trials. Incidence of cerebrovascular events was not an endpoint of interest in previous reviews that compared statins head-to-head in network meta-analyses.<sup>21,25–27</sup> Only one review indirectly compared statins (atorvastatin, pravastatin and simvastatin) in terms of major cerebrovascular events but this study was based on a small number of placebo-controlled trials, without making use of the valuable information from active-comparator trials of statins.<sup>28</sup>

The objective of our study was to systematically review the placebo-controlled and active-comparator trials of statins, and perform a multiple-treatments meta-analysis of individual statins in terms of their effect on major cerebrovascular events across all populations, in addition to secondary and primary prevention of cardiovascular disease separately.

## Methods

### Systematic review methods

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials to identify studies

published between 1 January 1985 and 1 January 2011. To comprehensively identify the active-comparator trials that were not included in previous meta-analyses of placebo-controlled trials, we used the search terms ‘atorvastatin’, ‘fluvastatin’, ‘simvastatin’, ‘lovastatin’, ‘pravastatin’, ‘rosuvastatin’, ‘cholesterol’, ‘cardiovascular disease’ and ‘HMG-CoA reductase inhibitors/therapeutic use’. Two researchers (BT and HT) independently performed abstract, title and full-text screening. A third researcher approved study selection (HN).

We included open-label and double-blind randomized controlled trials comparing one statin with another statin at therapeutic dose or with control (placebo, diet or usual care) for adults with, or at risk of developing, cardiovascular disease. We included trials of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin if they had more than 50 participants per trial arm, lasted longer than 4 weeks and reported major cerebrovascular events. Both fixed dose and titration designs were included. Per pre-defined criteria, we excluded trials conducted in patients with renal insufficiency.

Trials that included at least 80% of participants without established cardiovascular disease or reported data separately on a sole primary prevention group were categorized as primary prevention. Trials that included more than 80% of participants with established cardiovascular disease or reported data separately on a sole secondary prevention group were categorized as secondary prevention. All remaining trials were categorized as having a mixed patient population.

The primary outcome was major cerebrovascular events. In line with previous meta-analyses, we defined the composite of major cerebrovascular events as fatal- and non-fatal strokes and transient ischaemic attacks. As secondary endpoints, we evaluated fatal- and non-fatal strokes separately. For the analysis on non-fatal strokes, transient ischaemic attacks were not included.

We used a structured form to extract data on trial (reference, publication year, design features such as blinding and dosing regimen) and patient population characteristics (age, baseline LDL cholesterol, cardiovascular risk factors), and outcome measures. One researcher extracted data (HN) and another independently checked for accuracy (BT). To ensure quality, we checked the consistency of extracted data with previously published meta-analyses.

### Statistical analysis methods

We first qualitatively summarized included trials, describing the types of direct and indirect comparisons. For each pair-wise comparison between two

statins, we calculated the odds ratio (OR) with a 95% confidence interval. First, we performed classical pair-wise meta-analyses to synthesize studies that compared the same two statins using the DerSimonian Laird (random-effects) method.<sup>29</sup> The random-effects meta-analysis model assumed the observed estimates of treatment effect could vary across studies because of real differences in the treatment effect in each study and sampling variability (chance).<sup>30</sup> Forest plots of the relative treatment effects from the individual trials and pair-wise meta-analyses were visually inspected to search for heterogeneity. We also statistically inspected heterogeneity using the  $I^2$  statistic, which was used to estimate the percentage of total variation among studies that can be considered to be due to heterogeneity. We used rough thresholds of 25, 50 and 75% to define low, moderate and high heterogeneity, and investigated moderate and high heterogeneity by inspecting trial-level variables that may explain observed differences.

To determine the comparative effects of statins, we conducted multiple-treatments meta-analyses.<sup>31</sup> In these analyses, study-level relative treatment effects were combined using random-effects models within a Bayesian framework using Markov chain Monte Carlo methods.<sup>32,33</sup> We used the model developed by Dias *et al.*<sup>34</sup> for the National Institute of Health Clinical Excellence Decision Support Unit in the UK. This was based on modelling the outcomes in every treatment group of every study, and specifying the relations among the relative effects across studies making different comparisons.

To obtain a comprehensive estimate of the effect of statins in major cerebrovascular events, the multiple-treatments meta-analysis pooled all primary and secondary prevention trials in addition to trials with mixed patient populations. This analysis included all placebo-controlled and active-comparator trials eligible for inclusion in this review. We also performed separate analyses for the primary and secondary prevention populations, as categorized by the criteria mentioned earlier. For the base case analysis, we included trials at all doses. We separately evaluated the impact of dose differentials across the trials by excluding high-dose trials (80 mg/day for atorvastatin, fluvastatin, lovastatin, simvastatin and  $\geq 40$  mg/day for rosuvastatin) in a sensitivity analysis and evaluating the benefits of statins at comparable doses.

## Results

We included 61 trials (Figure 1), totalling 187 038 individuals. Overall, the average trial duration was

140 weeks (2.7 years). There were 51 two-armed placebo-controlled trials and the remaining 10 were two- or multi-armed active-comparator trials. There were 28 secondary prevention and 12 primary prevention trials. The remaining were in individuals who experienced acute coronary syndromes ( $n=8$ ) and those with mixed populations ( $n=13$ ). Of the 15 possible pair-wise comparisons between the six statins, only five were available for the major cerebrovascular events outcome. No trial directly compared all six statins to each other (Figure 2). Characteristics of included trials are summarized in Supplementary Table S1.

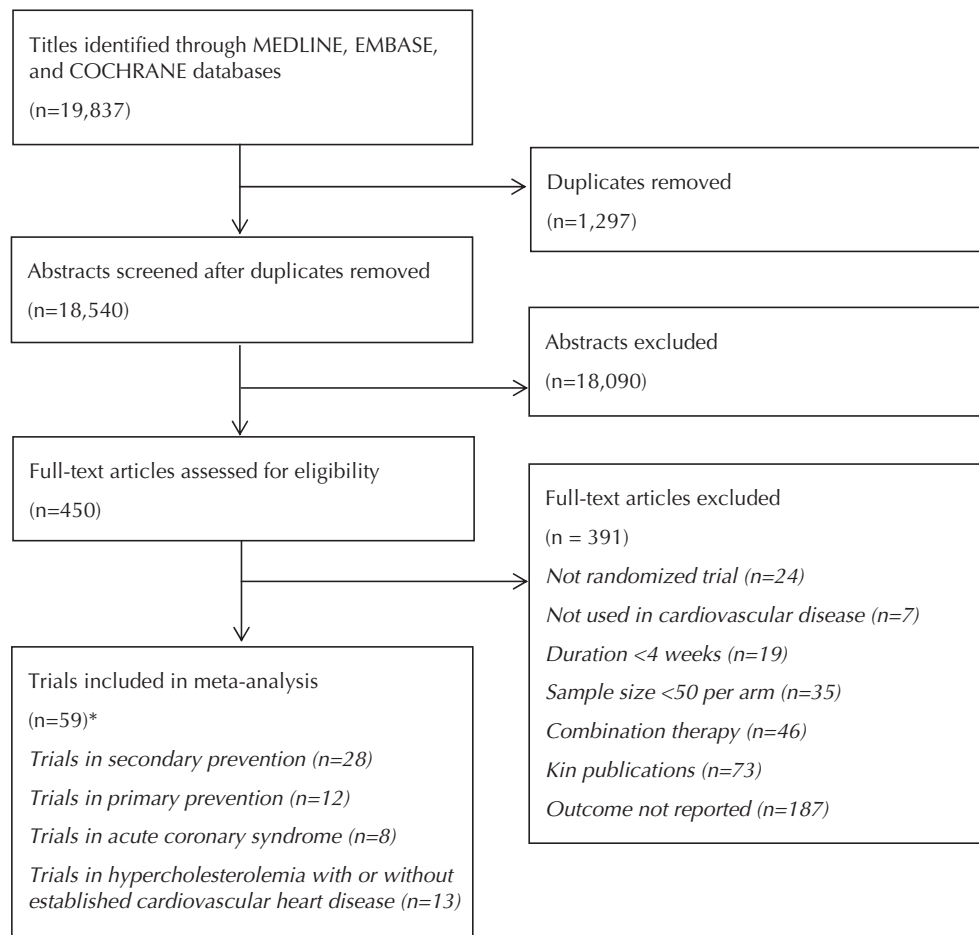
### Benefit of statin therapy vs. control: findings of the pair-wise meta-analyses

In the pair-wise meta-analysis of statin therapy vs. control across all populations, 171 731 individuals contributed information on 4533 events. Overall, statin therapy was associated with a reduction in the risk of major cerebrovascular events (OR: 0.82, 95% CI: 0.77, 0.87) when compared with control (Figure 3). Among statins, atorvastatin, pravastatin and simvastatin were associated with a significant reduction in major cerebrovascular events compared with the control, while fluvastatin, lovastatin and rosuvastatin were not.

In the secondary prevention population, statin therapy was associated with a significant reduction in major cerebrovascular events (OR: 0.83, 95% CI: 0.75, 0.91) when compared with control (Figure 3). Only atorvastatin resulted in significantly fewer events as compared with control in this population.

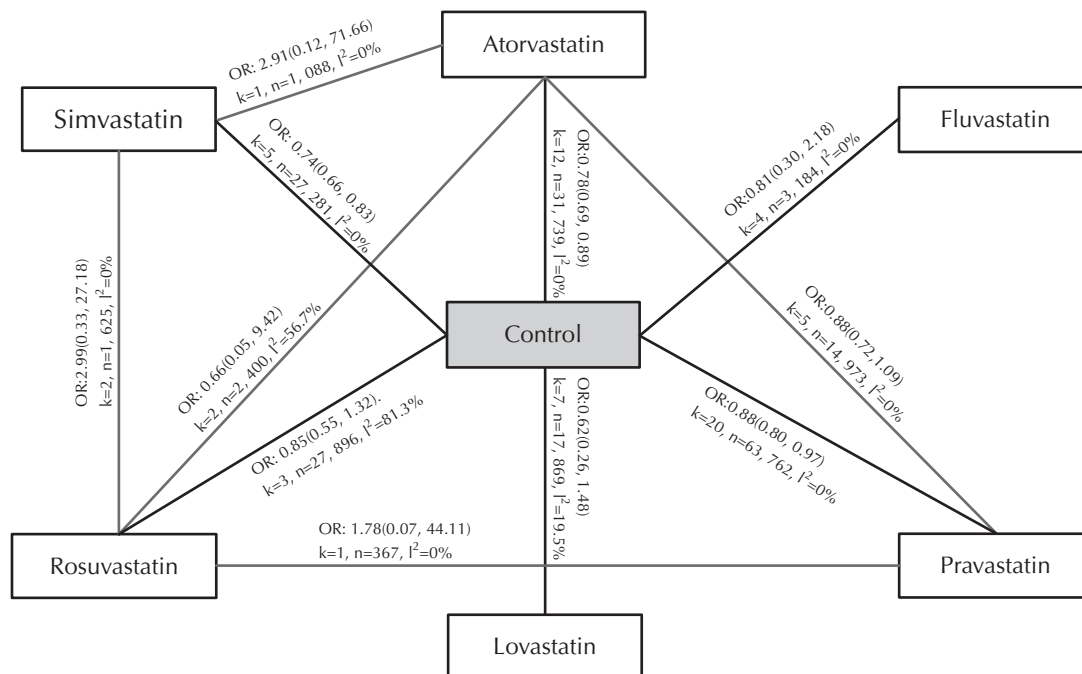
In the primary prevention population, statin therapy was associated with a significant reduction in major cerebrovascular events (OR: 0.80, 95% CI: 0.71, 0.91) (Figure 3). In this population, only atorvastatin and rosuvastatin had sufficient evidence for a significant benefit on major cerebrovascular events, while fluvastatin, lovastatin, pravastatin did not. Simvastatin did not have any trials in primary prevention.

Overall, statistical heterogeneity in pair-wise comparisons of statin therapy vs. control in all-cause mortality was low in analyses of primary prevention ( $I^2$ : 9.2%), secondary prevention ( $I^2$ : 0.0%) and all populations together ( $I^2$ : 0.0%). We observed high heterogeneity in pair-wise comparisons of rosuvastatin vs. control ( $I^2$ : 81.3%), mainly as a result of the differences in patient populations between JUPITER (primary prevention), GISSI-HF and CORONA (heart failure).



\* 61 trials when primary and secondary prevention populations within trials are considered separately.

**Figure 1.** Flow diagram of study identification and selection.



**Figure 2.** Network diagram of available comparisons.

## Comparative benefits of statins on major cerebrovascular events: findings of the multiple-treatments meta-analyses

In addition to the trials included in the pair-wise comparisons of statin therapy vs. control, there were 11 direct head-to-head statin comparisons, providing information on 20 072 participants. In the multiple-treatments meta-analysis, 61 placebo-controlled and active-comparator trials provided information for major cerebrovascular events analysis. In total, 187 038 individuals were included in this analysis, which provided information on 4913 events.

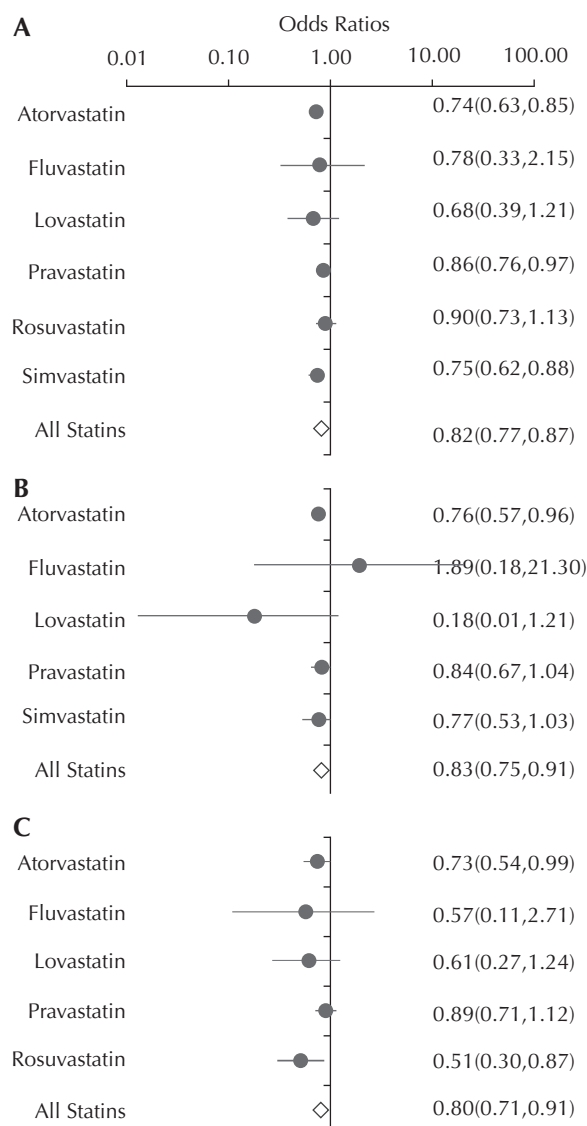
In this analysis, there were no significant differences among statins in terms of major cerebrovascular events when all trials of primary prevention,

secondary prevention and mixed patient populations were pooled (Figure 5). There were also no statistical differences among individual statins in terms of reducing the risk of major cerebrovascular events in primary and secondary prevention of cardiovascular disease.

The findings of the multiple-treatments meta-analysis were not sensitive to dose differentials across trials (Figure 4). When high-dose trials were excluded from the analysis, estimated comparative benefits of individuals were not materially different and there were no statistically meaningful differences between statins (Figure 5).

## Comparative benefits of statins on non-fatal and fatal strokes

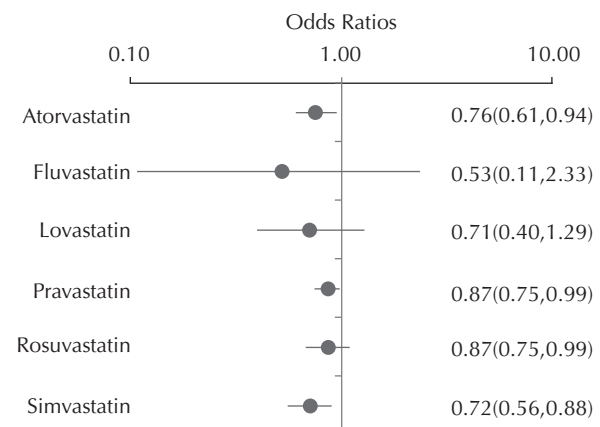
Across all populations, statins were effective in reducing the incidence of non-fatal strokes (OR: 0.77, 95% CI: 0.71, 0.85) as compared with control treatment (Figure 6). Only rosuvastatin (OR: 0.69, 95% CI: 0.44, 0.99) and simvastatin (OR: 0.69, 95% CI: 0.45, 0.96) had sufficient statistical power to show superiority over control treatment across all populations. Statins were not effective in reducing the risk of fatal strokes (OR: 0.96, 95% CI: 0.80, 1.15) although atorvastatin was independently superior to control treatment in preventing fatal strokes (OR: 0.49, 95% CI: 0.30, 0.80). There were no statistical differences between the individual statins.



**Figure 3.** Multiple-treatments meta-analysis findings: comparative effects of statins compared with control on major cerebrovascular events.

## Discussion

This multiple-treatments meta-analysis of 187 038 individuals provides evidence on the statistically and clinically meaningful benefits of statins in reducing the risk of major cerebrovascular events in both



**Figure 4.** Sensitivity analysis findings: comparative effects of statins compared with control on major cerebrovascular events.

<b>Atorvastatin</b>	0.94 (0.35, 2.26)	1.08 (0.60, 1.98)	0.86 (0.70, 1.04)	0.82 (0.63, 1.05)	0.99 (0.82, 1.21)
1.45 (0.32, 7.14)	<b>Fluvastatin</b>	1.14 (0.39, 3.82)	0.91 (0.37, 2.49)	0.86 (0.36, 2.30)	1.05 (0.43, 2.90)
1.07 (0.56, 1.98)	0.73 (0.13, 3.68)	<b>Lovastatin</b>	0.79 (0.44, 1.44)	0.76 (0.41, 1.38)	0.91 (0.50, 1.66)
0.87 (0.64, 1.20)	0.61 (0.12, 2.73)	0.81 (0.46, 1.49)	<b>Pravastatin</b>	0.95 (0.74, 1.23)	1.15 (0.94, 1.43)
0.87 (0.64, 1.20)	0.60 (0.12, 2.67)	0.82 (0.43, 1.55)	1.00 (0.75, 1.30)	<b>Rosuvastatin</b>	1.21 (0.93, 1.62)
1.05 (0.79, 1.47)	0.74 (0.15, 3.33)	0.99 (0.54, 1.86)	1.21 (0.94, 1.57)	1.21 (0.88, 1.69)	<b>Simvastatin</b>

**Figure 5.** Comparative effects of individual statins on major cerebrovascular events according to the multiple-treatments meta-analysis of all eligible trials (bottom half of figure) and sensitivity analysis excluding trials with high-dose formulations of statins (top half of the figure).

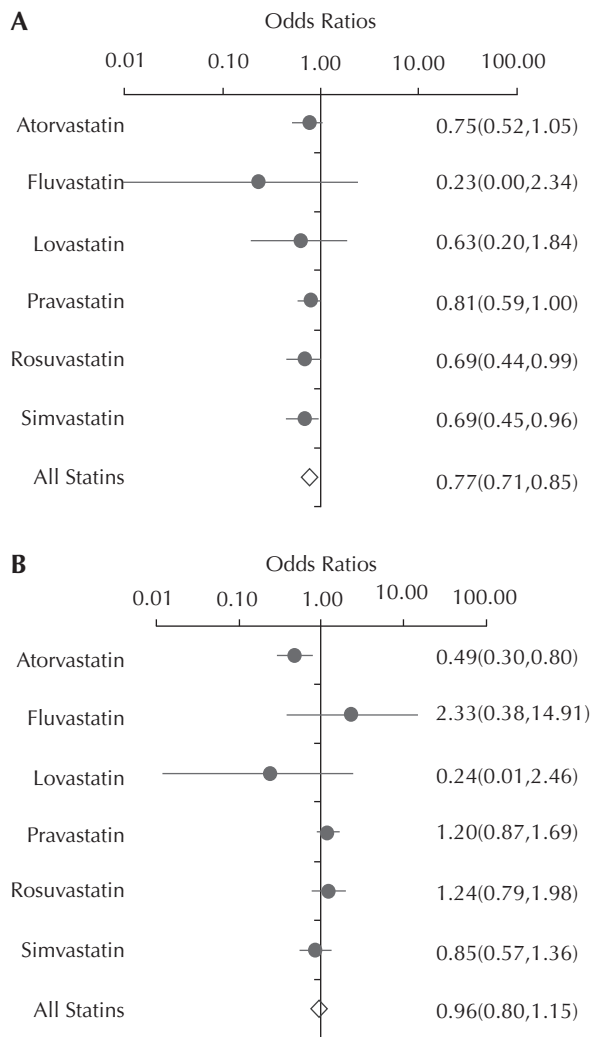
individuals with or without established cardiovascular disease. Overall, statins were associated with an 18% reduction in relative odds of major cerebrovascular events across all populations. Benefits of statins in reducing the relative odds of major cerebrovascular events by ~18% were consistent across primary and secondary prevention populations. Across all populations, given the lack of statistical difference between different statins, our analysis provided evidence to confirm the class effect of statins in preventing major cerebrovascular events.

Our overall findings reinforce and extend the results of previous meta-analyses on statin therapy. Previous reviews elucidated the importance of lipid management with statins in the prevention of strokes and found consistent evidence that would warrant advocating statin use for the prevention of incident strokes.<sup>35,36</sup> Clinical practice guidelines also recommend statin therapy in secondary prevention of stroke for patients with non-cardioembolic stroke.<sup>37,38</sup> As SPARCL was the only trial that investigated the benefits of statins for the secondary prevention of strokes in individuals with a history of transient ischaemic attack or stroke, we did not explore the comparative benefits of statins in this population separately.<sup>39</sup> Our base-case analysis in individuals with or without a history of established cardiovascular disease did not detect significant differences among individual statins. However, it remains a possibility that there are actual differences between individual statins which could not be detected in our analysis.

Indeed, although there were no statistical differences, our review suggested that the randomized trial evidence base for some statins was more robust and consistent than it was for others. This was particularly the case for atorvastatin and simvastatin. There was essentially no detectable heterogeneity across the trials of atorvastatin and simvastatin with consistent

evidence for their benefits in the prevention of major cerebrovascular events. Unlike simvastatin that did not have evidence in individuals with no history of cardiovascular disease, atorvastatin was able to reach statistical significance in both primary and secondary prevention populations (as well as across all populations) as compared with control treatment. Although atorvastatin led to a significant reduction in the risk of fatal strokes, unexpectedly, it was not associated with significantly fewer non-fatal strokes as compared with control. Trial evidence for fluvastatin and lovastatin was inconsistent across individuals with and without cardiovascular disease and there was large uncertainty around the benefits of these agents in the prevention of strokes. Finally, there was substantial heterogeneity in the evidence base for rosuvastatin. Given the small number of trials, JUPITER appeared to drive the pooled estimates for rosuvastatin, specifically for individuals without a history of cardiovascular disease.<sup>40</sup>

In addition to pair-wise meta-analyses that compared statins with control treatment, we also performed multiple-treatments meta-analysis, which is a relatively new method that differs from pair-wise meta-analysis by incorporating data from both direct (from head-to-head comparisons within trials) and indirect (from comparisons between trials) sources of evidence. Using this approach, we combined the results of placebo-controlled and active-comparator trials, allowing for more informed estimates of the relative effect of individual statins that have not been compared head-to-head in clinical trials. Our analysis differed from previous multiple-treatments meta-analyses in two important aspects. First, our review incorporated data from a comprehensive list of trials irrespective of placebo or active controls. Second, we provided comparative estimates separately for populations in primary and secondary prevention of cardiovascular disease.



**Figure 6.** Multiple-treatments meta-analysis findings: comparative effects of statins compared with control on non-fatal stroke and fatal stroke.

Findings of this study should be interpreted in light of its limitations. First, as a literature-based meta-analysis, our analysis shares the limitations of the published evidence base. There were only a few head-to-head trials of statins that were prospectively designed to capture differences in clinical outcomes as primary endpoints. Second, as a multiple-treatments meta-analysis combining direct and indirect sources of evidence, it remains a possibility that potential imbalances in the occurrence of effect modifiers across the contrasts impacted the results, potentially confounding the comparative estimates between statins.

In spite of these limitations, this study has important methodological strengths. Our review is the largest meta-analysis on the benefits of statin therapy on cerebrovascular events to date. We included 11 direct head-to-head statin comparisons, providing

information on additional 20 072 individuals that were not considered in prior meta-analyses on strokes. Our statistical models were appropriate for the evidence base as we did not detect any significant heterogeneity in the trial network. Although there was no considerable heterogeneity, we still used a random-effects model to take into account potential unexplained heterogeneity across the studies.

## Supplementary data

Supplementary material is available at *QJMED* online.

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*Conflict of interest:* Dr Fleurence is an employee of the Patient-Centered Outcomes Research Institute (PCORI). The views expressed in this article do not necessarily represent those of PCORI.

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## Comparative Tolerability and Harms of Individual Statins: A Study-Level Network Meta-Analysis of 246 955 Participants From 135 Randomized, Controlled Trials

Huseyin Naci, Jasper Brugts and Tony Ades

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# Comparative Tolerability and Harms of Individual Statins

## A Study-Level Network Meta-Analysis of 246 955 Participants From 135 Randomized, Controlled Trials

Huseyin Naci, MHS; Jasper Brugts, MD, PhD, MSc; Tony Ades, PhD

**Background**—Our objective was to estimate the comparative harms of individual statins using both placebo-controlled and active-comparator trials.

**Methods and Results**—We systematically reviewed randomized trials evaluating different statins in participants with and without cardiovascular disease. We performed random-effects pairwise and network meta-analyses to quantify the relative harms of individual statins. We included 55 two-armed placebo-controlled and 80 two- or multiarmed active-comparator trials including 246 955 individuals. According to pairwise meta-analyses, individual statins were not different than control in terms of myalgia, creatine kinase elevation, cancer, and discontinuations because of adverse events. Statins as a class resulted in significantly higher odds of diabetes mellitus (odds ratio, 1.09; 95% confidence interval, 1.02–1.16) and transaminase elevations (odds ratio, 1.51; 95% confidence interval, 1.24–1.84) compared with control. When individual statins were compared in network meta-analyses, there were numerous statistically detectable differences, favoring simvastatin and pravastatin. According to dose-level comparisons, individual statins resulted in higher odds of discontinuations with higher doses of atorvastatin and rosuvastatin. Similarly, higher doses of atorvastatin, fluvastatin, lovastatin, and simvastatin were associated with higher odds of transaminase elevations. Simvastatin at its highest doses was associated with creatine kinase elevations (odds ratio, 4.14; 95% credible interval, 1.08–16.24). Meta-regression analyses adjusting for study-level age at baseline, low-density lipoprotein cholesterol level, and publication year did not explain heterogeneity. There was no detectable inconsistency in the network.

**Conclusions**—As a class, adverse events associated with statin therapy are not common. Statins are not associated with cancer risk but do result in a higher odds of diabetes mellitus. Among individual statins, simvastatin and pravastatin seem safer and more tolerable than other statins. (*Circ Cardiovasc Qual Outcomes*. 2013;06:390-399.)

**Key Words:** cardiovascular disease ■ coronary disease ■ cardiovascular agents ■ Hydroxymethylglutaryl-CoA Reductase Inhibitors ■ adverse effects ■ meta-analysis ■ statins

Statins are widely used to prolong survival and reduce the occurrence of coronary and cerebrovascular events in patients with and without cardiovascular disease. Prior meta-analyses have demonstrated the effectiveness of statins for the primary and secondary prevention of cardiovascular disease,<sup>1–5</sup> with consistent benefits across subgroups, including the elderly,<sup>6</sup> women,<sup>7</sup> and individuals with diabetes mellitus.<sup>2</sup> Initially focused on secondary prevention, statin therapy has become more common because the limits of treatment have expanded over time to include people at progressively lower risk of developing cardiovascular disease.<sup>8</sup> As the number of individuals eligible for statin therapy continues to increase,<sup>9</sup> the comparative tolerability and harms of different statins warrant further investigation.

There is no comprehensive analysis on the comparative adverse event profiles of different statins, which builds on the totality of the existing randomized, controlled trial evidence

base. Although large-scale meta-analyses confirmed that the frequency of clinically significant side effects associated with statin therapy is low,<sup>10</sup> more research is needed to synthesize the evidence on a more diverse range of outcomes that are important for individuals receiving statins. These range from previously studied outcomes, such as cancer<sup>11–13</sup> and diabetes mellitus,<sup>14,15</sup> to muscle aches and clinically meaningful elevations in liver enzymes, which may be among factors contributing to nonadherence to long-term statin therapy.<sup>16,17</sup> Information regarding the relative tolerability and harms of different statins in the prevention of cardiovascular disease is needed to better inform patients, clinicians, and other healthcare decision makers.

Several reviews established the favorable safety profile of statins.<sup>18–22</sup> An important limitation of previous reviews is their focus on placebo-controlled trials, which did not take into account evidence from a large number of trials with direct head-to-head comparisons of statins. Equally important,

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## WHAT IS KNOWN

- The frequency of clinically significant side effects associated with statin therapy is low.
- There is no comprehensive analysis on the comparative adverse event profiles of different statins that builds on both placebo-controlled and active-comparator trials.

## WHAT THE STUDY ADDS

- Higher doses of some statins are associated with larger numbers of transaminase and creatine kinase elevations, and discontinuations because of adverse events.
- There are clinically meaningful differences among individual statins, with simvastatin and pravastatin likely to be ranked superior to their alternatives in terms of their safety profile.

previous reviews did not assess differences in dosages of individual statins across populations and did not compare statins at similar doses.

Our objective in this study was to systematically review and synthesize the totality of the randomized, controlled trial evidence on different statins and determine their comparative tolerability and harms across a range of populations eligible for statin therapy.

## Methods

### Systematic Review

Our search strategy was based on a publicly available protocol previously developed by the study authors to evaluate the comparative clinical benefits of statins.<sup>23</sup> We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials to identify studies published between January 1, 1985, and March 10, 2013. To identify the relevant literature, we developed a search strategy using the search terms atorvastatin, fluvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, cholesterol, cardiovascular disease, and hydroxymethylglutaryl-coenzyme A reductase inhibitors/therapeutic use. Our updated search in MEDLINE adopted Cochrane Collaboration's sensitivity and precision-maximizing strategy.<sup>24</sup> We searched for pitavastatin trials post hoc separately because our protocol did not include pitavastatin (protocol finalization coincided with the Food and Drug Administration approval of this agent). We also performed manual searches using the authors' files and reference lists from original communications and review articles to cross-check references. Two researchers (B.T., H.T.) independently performed abstract, title, and full-text screening. A third researcher approved study selection (H.N.).

We included open-label and double-blind randomized, controlled trials comparing one statin with another at any dose or with control (placebo, diet, or usual care) for adults with, or at risk of developing, cardiovascular disease. We included trials of atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin if they had >50 participants per trial arm and lasted >4 weeks based on prespecified inclusion and exclusion criteria.

Outcomes of interest were determined after protocol finalization. We included trials that reported tolerability (number of participants who discontinued the study medication because of adverse events), elevations in hepatic transaminases (number of participants with clinically meaningful elevations in either alanine aminotransferase or

aspartate aminotransferase, 3× baseline values as commonly defined by trial investigators), elevations in creatine kinase (CK; number of participants with clinically meaningful increases in baseline CK levels as defined by trial investigators, ranging from 3× to 10× higher than baseline concentrations), myalgia (number of individuals with muscle pain, as defined by trial investigators), myopathy (number of participants with 10× baseline CK levels associated with muscle symptoms), and rhabdomyolysis (number of participants with severe muscle damage, as diagnosed by trial investigators). In addition, we were interested in the incidence of cancer and diabetes mellitus (as defined by trial investigators), so trials reporting these outcomes were also eligible for inclusion. Both fixed dose and titration designs were included. As per our protocol, we excluded trials conducted in patients with renal insufficiency.

We used a structured form developed in MS Excel to extract data on trial and patient population characteristics and outcomes. We also extracted information on the methodological quality of included studies. In particular, information was collected on blinding, random sequence generation, allocation concealment, indications of incomplete outcome data, indications of selective reporting (possible for trials with published protocols), and industry sponsorship. One researcher extracted data (H.N.) and another independently checked for accuracy (B.T.).

### Statistical Analysis

We qualitatively summarized included trials, describing the types of direct and indirect comparisons and important clinical and trial design characteristics. For each pairwise comparison between 2 treatments, we calculated the relative effect with a 95% confidence interval (CI). We performed classical pairwise meta-analyses to synthesize studies that compared the same 2 treatments using the DerSimonian-Laird (random-effects) method. Forest plots of the relative treatment effects from the individual trials and pairwise meta-analyses were visually inspected to search for heterogeneity. We also statistically inspected heterogeneity using the  $I^2$  measure.

To determine the comparative tolerability and harms of individual statins, we conducted network meta-analyses, which are generalizations of indirect comparisons with >2 (or multiple pairs of) treatments being compared indirectly and ≥1 pair of treatments compared both directly and indirectly.<sup>25,26</sup> This type of analysis allowed for simultaneously combining the direct within-trial comparisons between 2 treatments (eg, atorvastatin versus control) with indirect comparisons constructed from trials that had 1 treatment in common (eg, atorvastatin versus control and simvastatin versus control).<sup>27</sup> This analysis preserved the within-trial randomized treatment comparison of each trial while combining all available comparisons between treatments. We combined study-level relative treatment effects using Bayesian Markov chain Monte Carlo methods in WinBUGS version 1.4.3. We used the model developed by Dias et al<sup>28</sup> for the UK National Institute of Health Clinical Excellence Decision Support Unit. This was based on modeling the outcomes in every treatment group of every study and specifying the relationships among the relative effects across studies making different comparisons, while taking into account the correlations between treatment effects within multiarm trials. Our models adopted random effects. The random-effects model took into account potential heterogeneity by assuming that each treatment was drawn from the same distribution, whose mean and variance were estimated from the data.<sup>29</sup> Additional details of our analytic approach are provided in the online-only Data Supplement Appendix.

Findings were reported in terms of odds ratios (OR). The difference between treatments was assessed on the basis of 95% CI in pairwise meta-analyses and 95% credible intervals (CrI) in network meta-analyses. CrIs may be interpreted as Bayesian equivalents of 95% CIs. The 95% CrI can be interpreted as indicating a 95% probability that the true OR falls within the reported range. If a 95% CrI does not include the null value 1.00, this can be interpreted as indicating <5% probability that there is no difference between the 2 comparators (referred to as significant difference between treatments hereafter). Given the Bayesian nature of the statistical analyses,  $P$  values are not estimated and reported for network meta-analyses.

We assessed the probability that each statin has the most favorable harm profile by calculating its treatment effect compared with control treatment and counting the proportion of iterations for which each statin has the highest treatment effect (ie, least harmful), the second highest, and so on. This approach took into account the magnitude of the estimated treatment effect, as well as the uncertainty around it. We graphically presented the distribution of ranking probabilities and estimated the surface under the cumulative ranking line for each statin.<sup>30</sup> The surface under the cumulative ranking line for each statin would be 1.00 when a treatment is certain to be the best (most favorable tolerability and harm profile) and 0.00 when a treatment is certain to be the worst (least favorable tolerability and harm profile). Ranking probabilities were estimated for the 4 outcomes with the most data (discontinuations because of adverse events, myalgia, elevations in hepatic transaminases, and elevations in CK levels) and combined in a composite measure with each of the 4 outcomes contributing 0.25 to the total ranking score of 1.00.

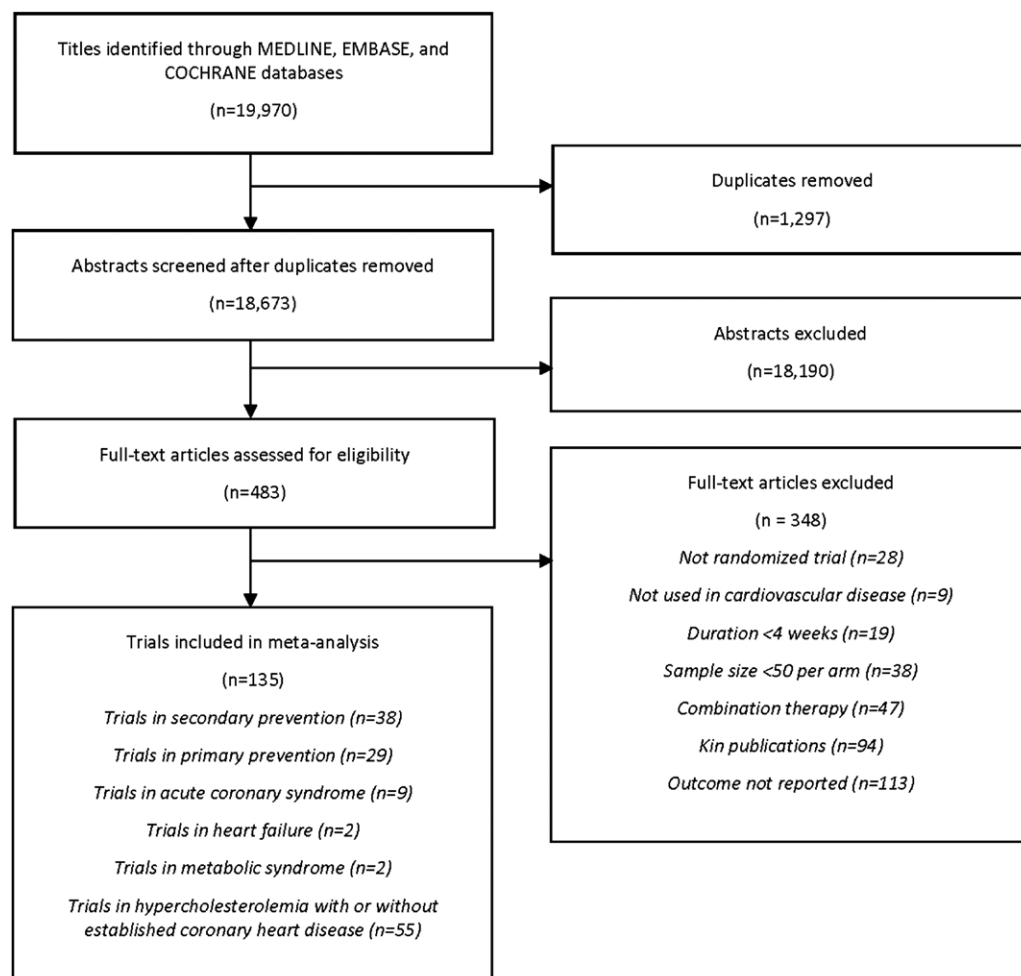
To obtain a comprehensive estimate of the comparative tolerability and harms of individual statins, our network meta-analysis pooled all primary and secondary prevention trials in addition to trials with mixed patient populations, including all placebo-controlled and active-comparator trials eligible for inclusion in this review. In subgroup analyses, we also investigated the comparative effects of individual statins in primary and secondary prevention separately.

Primary analyses were at the drug level (referred to as drug-level network meta-analyses hereafter), comparing individual statins to each other (eg, atorvastatin versus simvastatin). Sensitivity analyses were dose specific and explored the comparative harms of individual statins at different doses separately (referred to as dose level hereafter). Each statin-dose combination was treated as a different treatment, and no trends were fitted or assumed. The following daily doses were considered for

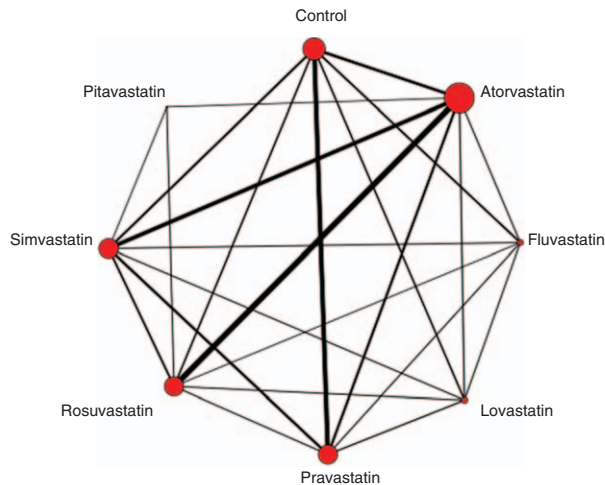
atorvastatin, lovastatin, pravastatin, and simvastatin:  $\leq 10$  mg,  $>10$  and  $\leq 20$  mg,  $>20$  and  $\leq 40$  mg, and  $>40$  mg. For fluvastatin, daily doses were  $\leq 20$  mg,  $>20$  and  $\leq 40$  mg, and  $>40$  mg. For rosuvastatin, the daily doses were  $\leq 5$  mg,  $>5$  and  $\leq 10$  mg,  $>10$  and  $\leq 20$  mg, and  $>20$  mg. For pitavastatin, 2 and 4 mg/d formulations were considered. All analyses were based on the total number of randomly assigned participants.

We investigated whether potential heterogeneity and inconsistency across the evidence base in the network meta-analysis of discontinuations, myalgia, transaminase elevations, and CK elevations could be explained by mean age at baseline, mean low-density lipoprotein cholesterol concentration at baseline, or the publication year of the trial using meta-regression analyses. All meta-regression analyses allowed for a common treatment-covariate interaction for each statin compared with control.<sup>31</sup> An additional sensitivity analysis excluded open-label trials and explored the comparative harms and tolerability of individual statins in double-blind trials.

For all outcomes, we also qualitatively evaluated the consistency of relative treatment effects obtained from an analysis of head-to-head trials with those obtained from an analysis combining both placebo-controlled and active-comparator trials. In particular, we first performed pairwise meta-analyses on all available direct comparisons (ie, direct evidence) and then compared the findings of these pairwise meta-analyses with the results of network meta-analysis (ie, mixed evidence). The consistency of the relative treatment effects was visually inspected for potential differences between estimates obtained from 2 sets of analyses (ie, direct and mixed estimates). We checked for discrepancy in terms of the direction of effect, as well as its magnitude, and confirmed that all 95% intervals greatly overlapped, which suggested adequate consistency. We also evaluated small-study effects using contour-enhanced funnel plots, which tested a composite hypothesis of publication and reporting bias, and chance.



**Figure 1.** Flow diagram of trial identification and selection.



**Figure 2.** Network of available comparisons for the drug-level analysis. Connecting lines indicate the existing direct pairwise comparisons between 2 treatments. The width of the lines is proportional to the number of pairwise comparisons between 2 treatments, and the size of every node is proportional to the number of participants.

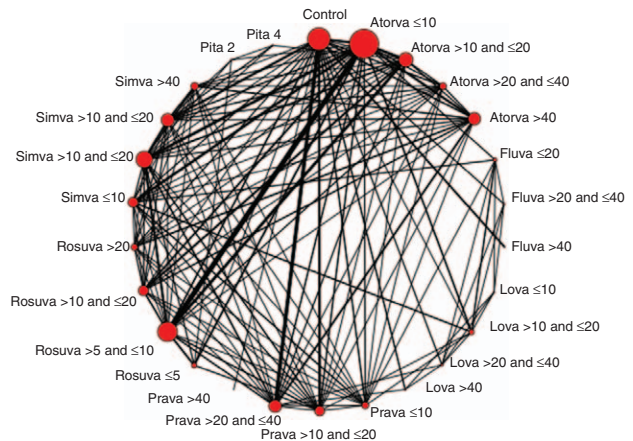
## Results

Our review included 135 trials (Figure 1), totaling 246 955 participants. Overall, the average trial follow-up was 68 weeks (1.3 years). There were 55 two-armed placebo-controlled trials, and the remaining 80 were 2-armed or multiarmed active-comparator trials. Of the 28 possible pairwise comparisons between the 8 treatments (7 statins and control), 22 were available. Most frequent comparisons occurred between pravastatin and placebo, atorvastatin and placebo, and rosuvastatin and atorvastatin. A total of 53 325 participants received atorvastatin, whereas 35 404 participants received simvastatin and 29 557 received pravastatin. No trial directly compared all 7 statins with each other for the drug-level comparison (Figure 2). Similarly, a small number of fluvastatin, lovastatin, and pitavastatin trials contributed to the dose-level network meta-analysis. No trial directly compared all statin-dose combinations with each other (Figure 3). Based on analyses on discontinuations because of adverse events, myalgia, transaminase elevations, and CK elevations, there was no evidence of differential effects between more precise and less precise trials according to contour-enhanced funnel plots (ie, no evidence of small-study effects).

The overall methodological quality of included trials was moderate. Older trials had lower methodological quality with inadequate sequence generation and treatment allocation concealment. A large number of trials did not report details about randomization procedures and allocation concealment. Only 11 trials had high methodological quality on all 6 items.

### Discontinuations Because of Adverse Events

According to the pairwise meta-analysis of placebo-controlled trials including 76 462 participants, statins as a class were not significantly different than control (OR, 0.95; 95% CI, 0.83–1.08;  $P$ , 21.9%). In the trials that directly compared individual statins head-to-head, simvastatin was significantly more tolerable than atorvastatin (OR, 0.61; 95%



**Figure 3.** Network of available comparisons for dose-specific analysis. Connecting lines indicate the existing direct pairwise comparisons between 2 treatments. The width of the lines is proportional to the number of pairwise comparisons between 2 treatments, and the size of every node is proportional to the number of participants.

CI, 0.42–0.89;  $P$ , 71.9%) and rosuvastatin (OR, 0.49; 95% CI, 0.27–0.88;  $P$ , 0.0%).

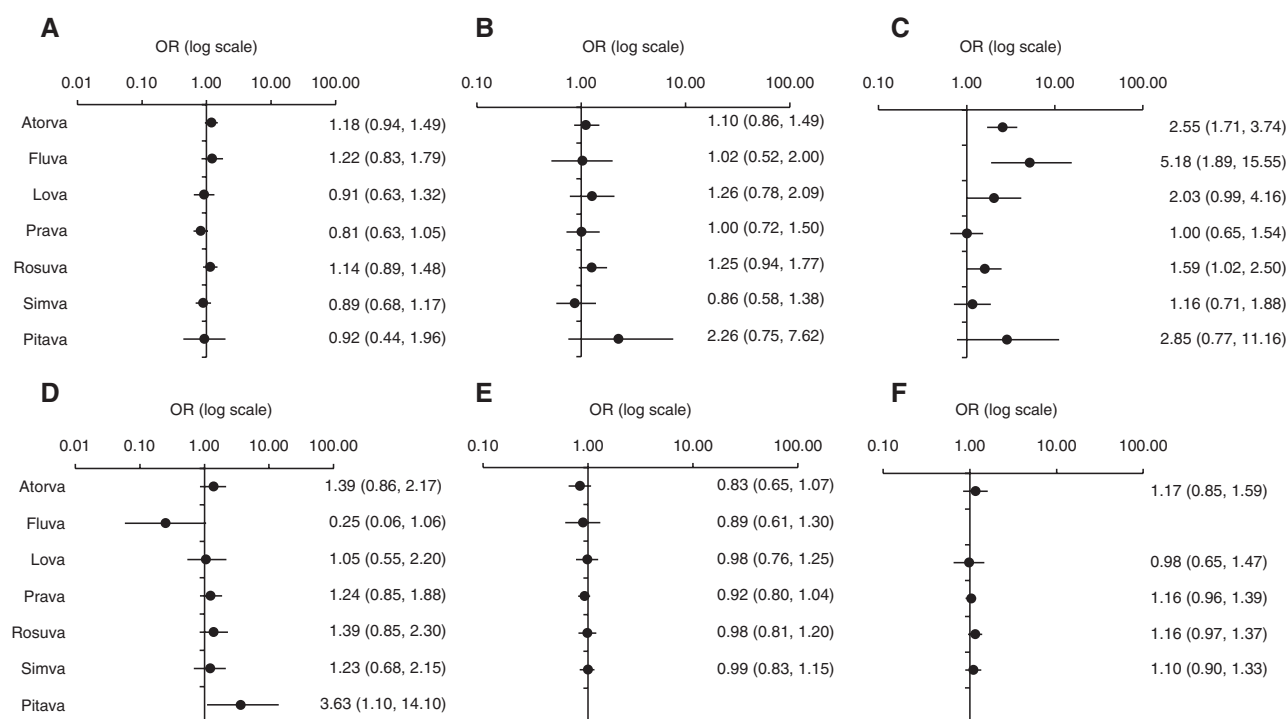
In the drug-level network meta-analysis of individual statins, 131 503 participants contributed information on 7811 events (6% of all participants). Individual statins were similar to control in terms of discontinuations because of adverse events (Figure 4A). When compared head-to-head, participants randomized to pravastatin (OR, 1.46; 95% CrI, 1.10–1.92) and simvastatin (OR, 1.34; 95% CrI, 1.06–1.69) were significantly less likely to stop treatment because of adverse events compared with those randomized to atorvastatin (Table 1).

The dose-level network meta-analysis of discontinuations because of adverse events included 151 823 participants, providing information on 8719 discontinuations. Atorvastatin at >20 and ≤40 mg/d (OR, 2.72; 95% CrI, 1.46–5.09) and atorvastatin at >40 mg/d (OR, 1.69; 95% CrI, 1.18–2.44) led to significantly more discontinuations compared with control. There was no strong dose-response relationship for most statin-dose combinations (higher doses did not necessarily result in higher discontinuation rates; Figure 5A).

### Myalgia

When the placebo-controlled trials of statins were pooled as a class in a pairwise meta-analysis including 43 531 participants, statins were not significantly different than control treatment (OR, 1.07; 95% CI, 0.89–1.29;  $P$ , 22.1%) in terms of myalgia incidence. The pairwise meta-analysis of head-to-head simvastatin versus atorvastatin trials showed that participants randomized to simvastatin had lower odds of experiencing myalgia compared with those receiving atorvastatin (OR, 0.56; 95% CI, 0.42–0.75;  $P$ , 0.0%).

Although the direction and magnitude of the difference between simvastatin and atorvastatin were similar in the drug-level network meta-analysis, there was greater variability around this estimate when all eligible direct and indirect trials were combined (OR, 0.78; 95% CrI, 0.55–1.13; reciprocals



**Figure 4.** Findings of drug-level network meta-analyses: effect of statins compared with control on (A) discontinuations because of adverse events, (B) occurrence of myalgia, (C) clinically meaningful elevation in hepatic transaminases, (D) clinically meaningful elevation in CK levels, (E) incidence of cancer, and (F) incidence of diabetes mellitus. There were no data to estimate cancer incidence with pitavastatin and diabetes mellitus incidence with fluvastatin and pitavastatin. CK indicates creatine kinase; OR, odds ratio.

reported in Table 1). According to the findings of the network meta-analysis including 84 391 participants with 1986 myalgia events (2% of all participants), there were no significant differences between individual statins.

In the dose-level network meta-analysis including 99 433 participants with 2533 events, there was a lack of an apparent dose-response relationship for myalgia (Figure 5B) with no statistically detectable differences between individual statin-dose combinations and control treatment.

### Transaminase Elevations

The pairwise meta-analysis of placebo-controlled trials including 122 665 participants showed that participants randomized to statins had significantly higher odds of experiencing alanine aminotransferase and aspartate aminotransferase

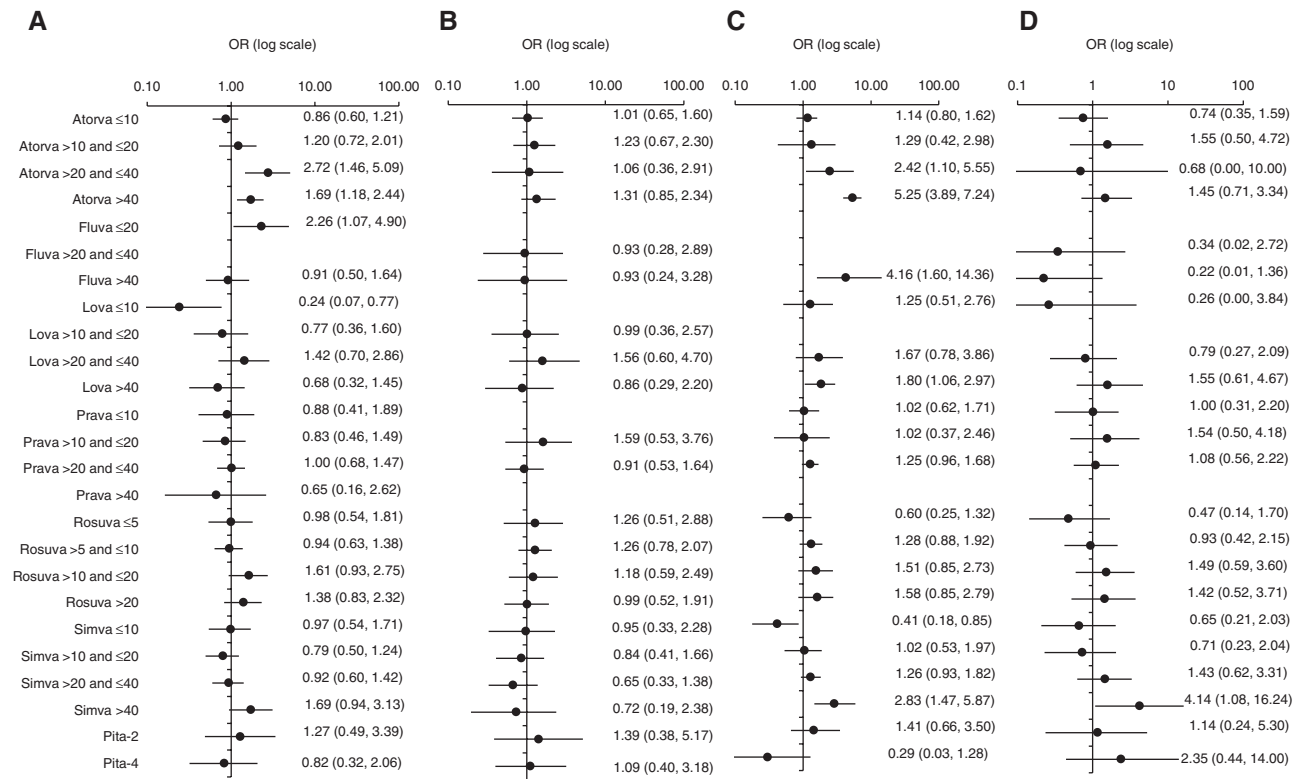
elevations compared with those randomized to control (OR, 1.51; 95% CI, 1.24–1.84;  $I^2$ , 52.3%). Among the trials that directly compared pravastatin and atorvastatin, participants randomized to pravastatin had significantly lower odds of transaminase elevations (OR, 0.27; 95% CI, 0.10–0.74;  $I^2$ , 61.3%).

In the drug-level network meta-analysis of individual statins, 165 534 participants contributed information on 2075 clinically meaningful elevations in hepatic transaminases (1% of all participants). Individuals randomized to atorvastatin (OR, 2.55; 95% CrI, 1.71–3.74) and fluvastatin (OR, 5.18; 95% CrI, 1.89–15.55) had higher odds of transaminase elevations (Figure 4C). When compared head-to-head, pravastatin (OR, 0.39; 95% CrI, 0.24–0.65), rosuvastatin (OR, 0.63; 95% CrI, 0.42–0.94), and simvastatin (OR, 0.45; 95% CrI, 0.28–0.73) had lower odds of transaminase elevations compared

**Table 1. Findings of Drug-Level Network Meta-Analyses, Showing the OR Comparing Statins (95% Credible Interval): Comparative Head-to-Head Effects of Individual Statins on Myalgia (top half of the table) and Discontinuations Because of Adverse Events (bottom half of the table)**

Atorvastatin	1.08 (0.56, 2.17)	0.87 (0.54, 1.46)	1.1 (0.77, 1.53)	0.88 (0.71, 1.08)	1.28 (0.88, 1.80)	0.49 (0.15, 1.42)
0.97 (0.64, 1.47)	Fluvastatin	0.81 (0.37, 1.71)	1.02 (0.48, 2.02)	0.82 (0.40, 1.58)	1.19 (0.56, 2.37)	0.46 (0.12, 1.52)
1.30 (0.87, 1.94)	1.33 (0.83, 2.14)	Lovastatin	1.26 (0.7, 2.15)	1.00 (0.58, 1.68)	1.46 (0.80, 2.54)	0.57 (0.15, 1.79)
1.46 (1.10, 1.92)	1.50 (0.97, 2.33)	1.13 (0.75, 1.7)	Pravastatin	0.80 (0.55, 1.19)	1.17 (0.74, 1.82)	0.45 (0.13, 1.35)
1.04 (0.85, 1.27)	1.07 (0.69, 1.65)	0.80 (0.52, 1.22)	0.71 (0.52, 0.97)	Rosuvastatin	1.46 (0.98, 2.14)	0.56 (0.17, 1.64)
1.34 (1.06, 1.69)	1.37 (0.89, 2.14)	1.03 (0.67, 1.57)	0.91 (0.67, 1.26)	1.28 (0.98, 1.69)	Simvastatin	0.39 (0.12, 1.12)
1.29 (0.62, 2.66)	1.32 (0.57, 3.06)	0.99 (0.43, 2.26)	0.88 (0.41, 1.89)	1.24 (0.59, 2.58)	0.96 (0.46, 2.02)	Pitavastatin

Comparisons between drugs should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, ORs <1 favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. OR indicates odds ratio.



**Figure 5.** Findings of dose-level network meta-analyses: effects of statin-dose combinations compared with control on (A) discontinuations because of adverse events, (B) occurrence of myalgia, (C) clinically meaningful elevation in hepatic transaminases, and (D) clinically meaningful elevation in CK levels. CK indicates creatine kinase; OR, odds ratio.

with atorvastatin (reciprocals reported in Table 2). Fluvastatin resulted in significantly higher odds of elevations than pravastatin (OR, 5.19; 95% CrI, 1.75–16.73), rosuvastatin (OR, 3.25; 95% CrI, 1.08–10.50), and simvastatin (OR, 4.50; 95% CrI, 1.49–14.19).

The dose-level network meta-analysis for clinically meaningful elevations in hepatic transaminases included 188 503 participants, providing information on 2298 events. There was a clear dose-response relationship for atorvastatin, lovastatin, and simvastatin, with higher doses resulting in higher odds of transaminase elevations (Figure 5C). Individuals receiving simvastatin at ≤10 mg/d had lower odds of experiencing transaminase elevations compared with those receiving control (OR, 0.41; 95% CrI, 0.18–0.85). Atorvastatin at >20 and ≤40 mg/d (OR, 2.42; 95% CrI, 1.10–5.55), atorvastatin at

>40 mg/d (OR, 5.25; 95% CrI, 3.89–7.24), fluvastatin at >40 mg/d (OR, 4.16; 95% CrI, 1.60–14.36), and simvastatin at >40 mg/d (OR, 2.83; 95% CrI, 1.47–5.87) resulted in significantly higher odds of elevations than control.

### CK Elevations

When the placebo-controlled trials of statins were pooled in a pairwise meta-analysis including 101 324 participants, statins as a class were not significantly different than control treatment (OR, 1.13; 95% CI, 0.85–1.51;  $P$ , 20.4%). In the drug-level network meta-analysis of individual statins, 127 571 participants provided information on 721 individuals with clinically meaningful CK elevations (0.6% of all participants). According to this analysis, pitavastatin resulted in significantly more CK elevations than control treatment (OR, 3.63; 95% CrI,

**Table 2.** Findings of Drug-Level Network Meta-Analyses: Comparative Head-to-Head Effects of Individual Statins on CK (top half of the table) and Transaminase Elevations (bottom half of the table).

Atorvastatin	5.59 (1.22, 25.52)	1.32 (0.54, 2.88)	1.13 (0.65, 1.78)	0.99 (0.64, 1.53)	1.13 (0.65, 1.97)	0.38 (0.10, 1.23)
0.49 (0.15, 1.42)	Fluvastatin	0.24 (0.05, 1.17)	0.20 (0.04, 0.88)	0.18 (0.04, 0.81)	0.20 (0.04, 0.94)	0.07 (0.01, 0.46)
1.26 (0.57, 2.73)	2.58 (0.76, 9.03)	Lovastatin	0.84 (0.39, 1.94)	0.76 (0.34, 1.85)	0.86 (0.37, 2.23)	0.29 (0.06, 1.18)
2.55 (1.54, 4.14)	5.19 (1.75, 16.73)	2.03 (0.90, 4.56)	Pravastatin	0.89 (0.51, 1.63)	1.01 (0.55, 2.00)	0.34 (0.09, 1.18)
1.60 (1.06, 2.38)	3.25 (1.08, 10.5)	1.27 (0.55, 2.93)	0.63 (0.36, 1.10)	Rosuvastatin	1.14 (0.62, 2.19)	0.38 (0.10, 1.23)
2.20 (1.36, 3.52)	4.50 (1.49, 14.19)	1.76 (0.75, 4.12)	0.87 (0.47, 1.57)	1.38 (0.79, 2.38)	Simvastatin	0.34 (0.08, 1.13)
0.89 (0.24, 3.23)	1.82 (0.34, 10.00)	0.71 (0.16, 3.13)	0.34 (0.08, 1.35)	0.55 (0.15, 2.04)	0.40 (0.10, 1.56)	Pitavastatin

CK, creatine kinase. Comparisons between drugs should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, ORs <1 favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. OR indicates odds ratio.

1.10–14.10; Figure 4D). Individuals randomized to fluvastatin had significantly lower odds of experiencing CK elevations compared with all other statins, except for lovastatin (Table 2).

The dose-level network meta-analysis for clinically meaningful elevations in baseline CK levels included 137 980 participants, providing information on 778 individuals who experienced elevations. There was a small dose-response relationship with lovastatin and simvastatin, with higher doses resulting in higher odds of elevations (Figure 4D). Simvastatin at >40 mg/d resulted in significantly higher odds of experiencing elevations compared with control treatment (OR, 4.14; 95% CrI, 1.08–16.24).

## Cancer

The pairwise meta-analysis of placebo-controlled trials including 100 523 participants showed that statins as a class were not significantly different than control treatment (OR, 0.96; 95% CrI, 0.91–1.02;  $P$ , 0.0%). Similarly, there was no evidence from the drug-level network meta-analyses that individual statins were different than control treatment on the basis of 5511 cancer occurrences among 105 450 participants (5.2% of all participants). There was also no evidence of potential head-to-head differences between individual statins (Table 3).

## Diabetes Mellitus

On the basis of placebo-controlled trials including 113 698 participants, the pairwise meta-analysis showed that statins as a class were statistically significantly different than control (OR, 1.09; 95% CrI, 1.02–1.16;  $P$ , 2.8%). According to placebo-controlled trials, rosuvastatin resulted in significantly higher odds of diabetes mellitus compared with control (OR, 1.16; 95% CI, 1.02–1.31;  $P$ , 0.0%). However, the drug-level network meta-analysis did not achieve statistical significance for any of the individual statins as a result of wider 95% CrIs (rosuvastatin had a similar effect size estimate in both pairwise and network meta-analyses; Figure 4D). Also, there were no statistically detectable differences between individual statins in terms of diabetes mellitus incidence (Table 3).

## Additional Outcomes

There was limited information on both myopathy and rhabdomyolysis outcomes. In the drug-level network meta-analysis, individual statins were not significantly different than control: atorvastatin (OR, 1.21; 95% CrI, 0.25–4.95), pravastatin (OR, 1.06; 95% CrI, 0.18–4.81), rosuvastatin (OR, 0.91; 95% CrI,

0.12–4.43), and simvastatin (OR, 1.23; 95% CrI, 0.29–4.21). There was no evidence of potential differences between individual statins in terms of myopathy outcomes (results not shown). Similarly, drug-level network meta-analysis showed that individual statins were not different than control treatment in terms of rhabdomyolysis: atorvastatin (OR, 1.33; 95% CrI, 0.31–6.92), pravastatin (OR, 0.20; 95% CrI, 0.00–11.15), rosuvastatin (OR, 0.19; 95% CrI, 0.00–9.22), and simvastatin (OR, 2.03; 95% CrI, 0.40–14.81). There were no statistically detectable differences between individual statins in terms of rhabdomyolysis.

When the individual statins were ranked in terms of the magnitude of the estimated treatment effect, as well as the uncertainty around it, pravastatin (0.71) and simvastatin (0.70) had the highest combined score out of a total of 1.00, suggesting that these statins had the most favorable tolerability and harm profile on the basis of discontinuations because of adverse events, myalgia, transaminase elevations, and CK elevations (Figure 6). Baseline low-density lipoprotein cholesterol concentration, baseline mean age of the study population, and publication year did not explain the observed heterogeneity in the evidence base. Estimate of between-study heterogeneity in the drug-level network meta-analyses did not decrease in meta-regression analyses. According to the sensitivity analyses, findings from the base-case network meta-analyses did not change when adjusting for baseline low-density lipoprotein cholesterol concentration, mean age, and publication year in meta-regression analyses, with statistically nonsignificant coefficients (results provided in the online-only Data Supplement Appendix). Limiting the analysis to double-blind trials also did not change the observed ORs. Although small sample size was a limitation of subgroup analyses, we did not obtain materially different comparative harm and tolerability estimates for individual statins in primary versus secondary prevention populations (results provided in the online-only Data Supplement Appendix).

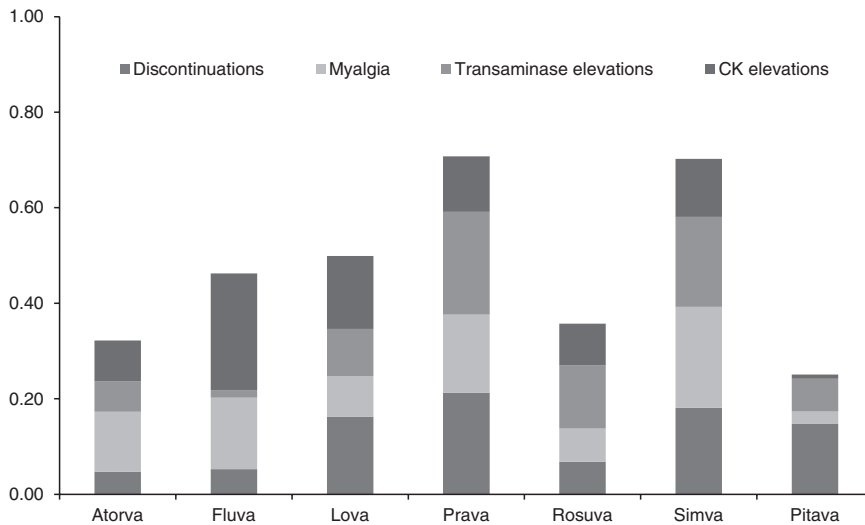
## Discussion

This network meta-analysis of 246 955 participants provides evidence on the comparative tolerability and harms of individual statins using both placebo-controlled and active-comparator trials. Overall, statins as a class are associated with an increased risk of diabetes mellitus and hepatic transaminase elevations, with no statistically detectable effect on myalgia, myopathy, rhabdomyolysis, and cancer. Across the totality of the evidence base, higher doses of some statins result in higher

**Table 3. Findings of Drug-Level Network Meta-Analyses: Comparative Head- to-Head Effects of Individual Statins on Diabetes (top half of the table) and Cancer (bottom half of the table)**

Atorvastatin	-	1.18 (0.71, 1.99)	1.12 (0.79, 1.62)	1.01 (0.69, 1.47)	1.06 (0.72, 1.57)
0.94 (0.59, 1.47)	Fluvastatin	-	-	-	-
0.86 (0.60, 1.20)	0.91 (0.58, 1.43)	Lovastatin	0.95 (0.62, 1.46)	0.85 (0.54, 1.33)	0.90 (0.56, 1.41)
0.90 (0.69, 1.20)	0.97 (0.65, 1.45)	1.06 (0.81, 1.42)	Pravastatin	0.90 (0.70, 1.12)	0.94 (0.72, 1.21)
0.84 (0.62, 1.16)	0.90 (0.58, 1.39)	0.99 (0.73, 1.36)	0.94 (0.73, 1.19)	Rosuvastatin	1.05 (0.80, 1.40)
0.84 (0.66, 1.08)	0.90 (0.60, 1.37)	0.98 (0.75, 1.34)	0.93 (0.77, 1.15)	0.99 (0.78, 1.30)	Simvastatin

Comparisons between drugs should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, ORs <1 favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. OR indicates odds ratio.



**Figure 6.** Overall ranking of individual statins in placebo-controlled and active-comparator trials of participants by their overall probability to be the best treatment in terms of discontinuations because of adverse events, myalgia, hepatic transaminase elevation, and CK elevation. In addition to the overall score for each statin, the relative contribution of each of the 4 outcomes to the overall score is also shown. Each statin was scored with points up to a maximum of 0.25 for each outcome (overall maximum score: 1.00). Higher scores indicate a better tolerability and safety profile. CK indicates creatine kinase.

odds of experiencing transaminase elevations, CK elevations, and discontinuations because of adverse events. When compared head-to-head in network meta-analyses, there are differences among individual statins, with simvastatin and pravastatin likely to be ranked superior to their alternatives in terms of their safety profile.

Although the benefits of statins for individuals with established cardiovascular disease are well documented,<sup>9</sup> their effect in individuals free of cardiovascular disease has been disputed.<sup>8,32–34</sup> Recent meta-analyses based on both individual patient-level data<sup>4</sup> and study-level reports<sup>5</sup> confirm that all-cause mortality benefits of statins in the primary prevention setting are clinically and statistically significant. These recent findings provide supporting evidence for initiating statin therapy in individuals who are at an increased risk of developing cardiovascular disease. Nevertheless, expanding the limits of statin therapy to a wider population of individuals may have important safety implications. Although rare, adverse events associated with statin therapy range from mild to moderate and seem to increase with treatment intensity. With notable exceptions,<sup>35</sup> randomized trial evidence on the long-term safety of individual statin treatments remains limited.

Our review confirms the findings of previous pairwise meta-analyses in that statins as a class are associated with higher odds of developing diabetes mellitus<sup>15</sup> and experiencing hepatic transaminase elevations.<sup>36</sup> There is a lack of evidence that statins are associated with an increased risk of developing cancers. Although our review did not find statistical evidence of myopathy, this may be because of an underdetection of muscle toxicity in clinical trials.<sup>37–39</sup>

At the population level, mortality and cardiovascular benefits of statin therapy greatly outweigh its potential harms, even taking into account the recent finding that statin use is associated with a modest increase in diabetes mellitus incidence.<sup>40</sup> At the individual level, however, there may be a risk of exposing a large group of individuals to the (primarily minor) harms of statin therapy for the benefit of a smaller number of individuals. This brings into sharp focus the importance of correctly identifying the set of individuals who stand to benefit from statin therapy. There are emerging tools that

can be used to predict personalized long-term harms and benefits associated with statin therapy.<sup>41</sup>

Available statins differ to a various extent in pharmacological properties, and it would be expected that they differ in terms of their clinical efficacy.<sup>42,43</sup> Nonetheless, their comparative harms had not been evaluated in a comprehensive manner in previous reviews. In addition to pairwise meta-analysis that compared statins with control treatment, we performed network meta-analysis, which is a relatively new method that differs from pairwise meta-analysis by incorporating data from both direct (from trials that include a specific pairwise comparison) and indirect (from a network of trials that do not include that comparison) sources of evidence. We previously used this method to compare individual statins in terms of their cholesterol-lowering effects, as well as their effects on deaths, coronary events, and cerebrovascular events.<sup>44–46</sup>

Our findings show that there are statistically detectable differences between individual statins in terms of their tolerability, hepatic transaminase elevations, and CK elevations. At the drug level, individuals receiving simvastatin and pravastatin seem to have the lowest odds of experiencing myalgia, transaminase and CK elevations, and discontinuations because of adverse events.

Our dose-specific analysis parallels the findings of previous meta-analyses in that more intensive statin therapy is associated with greater risk of harm and less favorable tolerability compared with lower doses.<sup>19,47–49</sup> Similar to previous studies, we observed a general dose–response relationship across placebo-controlled and active-comparator trials in terms of discontinuations because of adverse events, transaminase elevations, and CK elevations.

As with any meta-analysis, our network meta-analysis required an assumption of similarity across the pooled set of trials in terms of patient population and trial characteristics. More specifically, we assumed that the distribution of relative treatment effect modifiers (eg, baseline cholesterol levels) was balanced across different treatment comparisons in the evidence network. An imbalance in the distribution of these variables in a single randomized, controlled trial would result in within-trial heterogeneity; an imbalance across

trials would result in between-study heterogeneity in pairwise meta-analyses; and an imbalance across different treatment comparisons would result in inconsistency in network meta-analyses, potentially biasing the results. To account for such imbalances, we evaluated several study-level characteristics in the meta-regression analyses. Specifically, our analyses suggested that baseline mean age, low-density lipoprotein cholesterol concentration, and trial publication year did not have an impact on the observed findings.

Findings of this study should be interpreted in light of its limitations. First, as a literature-based meta-analysis, our analysis shares the limitations of the published evidence base. The quality of included trials was moderate, with older trials being more prone to bias than newer trials. Second, given the large volume of available studies in the literature, our meta-analysis did not use individual patient-level data, which would have advantages when exploring potential differences across relative treatment effect modifiers. Third, although there was no evidence of small-study effects, there was an apparent asymmetry in the evidence network where specific interventions seem to be avoided (eg, fluvastatin). For instance, the relative effect of fluvastatin on CK elevations was estimated on the basis of 8 events observed in 4 trials including 2646 participants. Similarly, there were only 4 trials of fluvastatin, which reported hepatic transaminase elevations. As expected, the evidence base for pitavastatin was also sparse. Although pitavastatin was recently approved by the Food and Drug Administration, it has been in use in other settings since 2003 (most notably in Japan and South Korea) without a corresponding evidence base in the English language literature. Fourth, there was considerable heterogeneity across various pairwise meta-analyses of statins versus control, particularly for hepatic transaminase elevations. It remains a possibility that our analysis did not fully account for heterogeneity as a result of unobserved or unmeasured factors. However, we used a random-effects model, and our analyses took into account potential unexplained heterogeneity across the studies. We also performed meta-regressions to further evaluate heterogeneity and inconsistency and did not detect a significant effect of study-level characteristics.

Despite these limitations, our study has important methodological strengths. First, this review is the largest meta-analysis on the harms of statin therapy to date, including almost a quarter million trial participants. Second, we incorporated data from a comprehensive list of trials, irrespective of placebo or active controls, including all clinically used statins. In total, we included 80 active-comparator trials with or without a placebo or usual care arm. Third, we evaluated the dose-comparative harms of individual statins.

Our findings have important clinical implications. First, there is strong evidence that statins as a class are generally safe with uncommon side effects. According to the findings of this comprehensive analysis, there is consistently strong evidence on the comparatively favorable side effect profile of simvastatin and pravastatin, particularly at low-to-moderate doses, which should be favored in clinical practice. This meta-analysis sheds new light on the discussion of the relationship between statins and diabetes mellitus incidence and confirms that statin use is not associated with cancer incidence. Finally, we acknowledge the complex nature of making prescribing

decisions and urge prescribers to consider the findings of this analysis in light of the comparative benefit profiles of individual statins in preventing all-cause mortality in addition to cardiovascular and cerebrovascular events.<sup>44–46</sup>

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## Disclosures

None.

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## SUPPLEMENTAL MATERIAL

### Analytic Approach Details

For all binary outcomes of interest, we assumed that the number of events per trial arm had a binomial distribution. We used the logit function to link the probability of an event in each arm of each trial, the trial-specific baseline effect (treatment effect of the control arm), and the relative treatment effect of the treatment compared with control. We set noninformative (i.e., vague or flat) priors  $N(0, 1002)$  for trial specific baselines and relative treatment effects. In our random-effects models, we also set noninformative priors for the between-trial variance  $[\sigma \sim \text{Uniform}(0,2)]$ .

All analyses employed a long burn-in period (50,000 iterations) and follow-up period (80,000-100,000 iterations) to allow for convergence. Trace plots for key parameters for each analysis were systematically reviewed (i.e., visually inspected) to assess convergence in terms of stability.

A systematic procedure was followed to ensure that the choice of initial values used in WinBugs models did not have a substantial impact on the findings. We evaluated the convergence of models in WinBugs by performing 3-chain analyses with widely dispersed starting values, and evaluating their convergence using the Brooks-Gelman-Rubin (BGR) diagnostic plots.

Sensitivity of the findings to prior distributions was not evaluated for any of the analyses presented in this paper. However, we performed such sensitivity analyses by varying the prior distributions from less informative to more informative values and examining the variability observed in the credibility intervals of point estimates for all-cause mortality and major coronary event outcomes, as reported previously (Naci H et al., Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials, *Eur J Prev Cardiol*, 2013). We did not have any reason to expect that the models used for the analyses in this paper would behave differently in terms of their sensitivity to priors.

We formally evaluated the goodness of fit of our models using the total residual deviance (posterior mean of the deviance under a given model minus the deviance for the saturated model). In each model, we compared the residual deviance with the total number of data points in the dataset. We expected that each data point would contribute about 1 point to the posterior mean deviance. In cases where total residual deviance was considerably higher than the number of individual data points (i.e., 5-7 points), the difference was due to the large number of data points with zero cells. As expected, models could not predict a zero cell since probabilities at zero or one were ruled out, which resulted in the total residual deviance estimates to appear large when there were a large number of zero cells.

#### Assessment of model fit for the drug-level analysis

	Effective number of parameters, pD	Total residual deviance
Discontinuations due to adverse events	155	235
Myalgia	76	141
Transaminase elevations	105	158
CK elevations	63	117

#### Assessment of model fit for the dose-level analysis

	Effective number of parameters, pD	Total residual deviance
Discontinuations due to adverse events	208	319
Myalgia	110	172
Transaminase elevations	117	202
CK elevations	90	142

Our inconsistency assessment for the outcomes evaluated in this paper was based on qualitative criteria. In a stepwise manner, we first performed pairwise meta-analyses on all available direct comparisons. We then compared the findings of these pairwise meta-analyses with the results of network meta-analysis findings (what we refer to as “mixed” findings, combining direct and indirect evidence). We considered this approach to be adequate since we previously performed a more formal statistical evaluation of inconsistency in this evidence network (Naci H et al., Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials, *Eur J Prev Cardiol*, 2013). In particular, we explored potential inconsistency in the evidence network for all-cause mortality and major coronary network outcomes using an approach developed by Salanti and colleagues (and implemented in R). For these clinical benefit outcomes, we identified all possible first-order (triangles) and second-order (quadrilaterals) closed loops formed by the network of statins. For each closed loop we then estimated the difference between the direct and indirect evidence. As a rough guide for the presence of inconsistency, we evaluated the “inconsistency factor” and its uncertainty within each closed loop formed in the network. This assessment did not find any evidence of inconsistency in our evidence network.

## COMMENTARY

# Assessing comparative effectiveness of new drugs before approval using prospective network meta-analyses

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## 1. Introduction

Comparative efficacy and safety data are often lacking at the time of new drug approval for market entry. Regulatory agencies in the United States (the Food and Drug Administration [FDA]) and the European Union (the European Medicines Agency [EMA]) often evaluate each new drug on its own (often in placebo-controlled trials), and without comparative assessments against other available drugs [1].

The existing lack of comparative evidence at the time of new drug approval poses important challenges for patients, prescribers, payers, and the wider health care systems. Prescribers and patients do not have adequate information on the comparative clinical efficacy and safety of various alternative drugs for a given condition, which can lead to widespread adoption of treatments, with potentially inferior efficacy or safety relative to existing alternatives [2–5].

Recent proposals call for requiring comparative evidence at the time of marketing authorization decisions [6–8]. In this article, we propose an approach that uses prospective network meta-analysis (NMA) to expand the comparative clinical efficacy and safety evidence available at the time of new drug approval. We characterize how prospective NMA can facilitate the comparison of new drugs with their alternatives in the regulatory setting.

## 2. Pairwise and network meta-analysis

Pairwise meta-analysis (PMA) is a statistical tool for pooling the results of multiple comparable, randomized, controlled trials that compare the same two interventions directly [9]. The main consideration when performing and interpreting PMA is similarity (also known as homogeneity) across the pooled set of studies in terms of trial and patient population characteristics [10].

In the regulatory setting, PMA addresses essential questions such as safety concerns. For example, a series of recent PMAs was pivotal in identifying safety concerns for rosiglitazone [11,12]. In the United States, these concerns also contributed to the FDA's *Guidance for Industry* [13], which encourages manufacturers of new antidiabetic drugs to perform prospective PMAs to evaluate cardiovascular events associated with their products. In Europe, the EMA's Committee for Medicinal Products for Human Use frequently refers to findings of PMAs to evaluate the evolving benefit–harm balance of drug options on the market. In one recent example, the Committee for Medicinal Products for Human Use referred to the findings of PMAs in its assessment report for nonsteroidal anti-inflammatory drugs and cardiovascular risk [14].

In conditions with several drug options, PMA is limited by the relatively small number (or the lack) of trials that compare a particular pair of drugs directly. By definition, PMA is incapable of comparing multiple active comparators simultaneously. When there are multiple drugs, performing separate PMAs for each comparison becomes impractical (or impossible, if there are no trials that include the comparison of interest) [15]. Focusing on two drugs at a time, such an approach also does not take into account adequately the correlation structure in multiarm trials [16].

NMA is a relatively new method that differs from PMA by incorporating data from both direct (from trials that include a specific pairwise comparison) and indirect (from a network of trials that do not include that comparison) sources of evidence [15]. NMA is capable of evaluating the relative efficacy and safety of two or more drugs [17,18]. The latest statistical methods facilitate the comparison of treatments in any network structure and complexity, as long as treatments are connected in a network (i.e., all treatments are connected to each other either directly or indirectly) [19–21].

As with PMA, NMA requires an assumption of similarity across the pooled set of trials in terms of patient population and trial characteristics [16]. Significant deviations in trial characteristics, such as outcome definition and

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assessment or patient population, can violate the similarity assumptions [22]. This may result in biased estimates of comparative efficacy and safety when the factors responsible for differences across trial or patient population characteristics are relative treatment effect modifiers [23]. When both direct and indirect evidence is available, it is essential to check whether they are consistent [24–26]. Occasionally, conflicting results are obtained from direct and indirect comparisons, which suggests the possibility of imbalances in the distribution of relative treatment effect modifiers [27]. The similarity assumption in the NMA can be explored using metaregression and subgroup analyses [28]. A more detailed overview of NMA methods is provided by Dias et al. [29].

### 3. Regulatory process for new drugs and the proposed role of NMA

NMA could be used to estimate the efficacy and safety of new drugs relative to existing alternatives at the time of market entry. These estimates could be used during regulatory assessment for market authorization of new drugs.

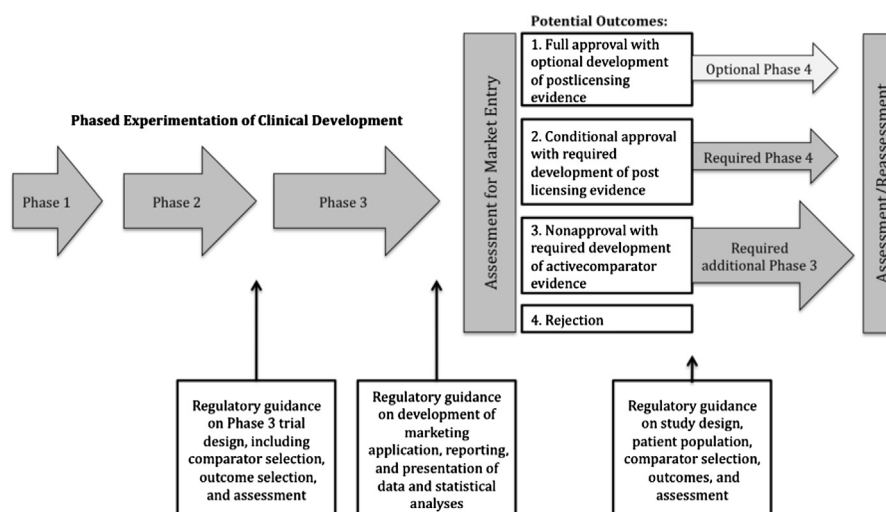
An overview of the current regulatory process is provided in Fig. 1. There are three phases of experimentation before the regulatory assessment of new drugs for market entry [30,31]. During phase 1, an investigational drug is tested in a small number of healthy volunteers to explore its toxicity profile. During phase 2, trials are performed that involve a larger number of individuals (100–300) with a given condition or disease (1) to assess whether the drug provides the intended clinical benefits and (2) to monitor short-term side effects. During phase 3 trials, the drug is tested in a larger group of individuals (600–3,000) with a given condition or disease to establish its clinical efficacy

and safety. Regulatory assessment for market authorization follows the completion of phase 3.

As shown in Fig. 1, regulators are involved in clinical development of new therapies. In the case of the FDA, an end-of-phase 2 meeting is arranged to determine the safety of proceeding to phase 3, to evaluate the phase 3 trial plan, and to identify any additional information necessary to support regulatory assessment after the completion of phase 3 [32]. After the completion of phase 3, regulators and manufacturers have another opportunity to discuss a number of topics with regard to the marketing application, including the appropriate methods to use for statistical analysis of the data, and to discuss the best approach to the presentation of data in the marketing application. These processes are closely paralleled by the regulatory involvement in clinical development by the EMA in Europe [33].

At the time of regulatory assessment for market authorization, NMA could be used to estimate the comparative efficacy and safety of the new drug and its existing alternatives. In cases when no active comparator trials exist, NMA could generate estimates of comparative efficacy and safety. In cases when both placebo-controlled and active comparator trials exist, NMA could combine the findings of the direct comparisons with those from indirect comparisons for support of superiority or noninferiority claims. In cases when only active comparator trials exist, these could be combined in NMA as long as drugs are compared with each other in a connected network.

Active comparator trials and, in particular, noninferiority designs, are increasingly common in regulatory settings [34]. Noninferiority trials are designed to assess whether a new drug is not worse than an active control by more than a specified noninferiority margin [35]. In contrast to superiority trials, which are successful in showing a difference between drugs, noninferiority trials cannot establish that the active control had its expected effect in the study



**Fig. 1.** A simplified overview of regulatory involvement during the phased experimentation of drug development, and potential outcomes of market entry assessment.

(i.e., that the trial had assay sensitivity) unless they also have a placebo arm (which is often not feasible) [36]. Non-inferiority trials without a placebo arm require an assumption based on the results of preceding trials that the active control had its expected effect in the study. NMA can be particularly helpful in these situations.

First, in cases when the drugs are not connected in a network as a result of a lack of placebo or other common comparator, external trial evidence could be used to compare drugs with each other in a network. Consider a hypothetical scenario with four drugs of interest: A, B, C, and D. If the existing trials compare separately drug A vs. drug B and drug C vs. drug D, NMA methods cannot be used to compare all drugs, given the lack of a connected network. If there are trials that compare drug B vs. drug E and drug D vs. drug E, however, all treatments can be connected in a network (connected through drug E), and compared in NMA.

Second, external evidence on placebo or historical controls could be incorporated in NMAs to provide information on assay sensitivity and to establish historical evidence of sensitivity to drug effects [36]. This involves identifying trials that used a specific active control (in general, the one that is also used during the noninferiority trial) that showed this treatment to be superior to placebo (or some other treatment). These findings can be incorporated in an NMA to allow for a reliable estimate of the drug's effect size compared with placebo in those past studies.

#### 4. NMA and market authorization decisions

At the time of regulatory assessments for market entry, NMA could potentially suggest that a new drug is superior, equivalent (or noninferior), or inferior to one or more existing alternatives. Superiority could be determined via more beneficial (e.g., more efficacy at the primary end point) and/or less harmful (e.g., less discontinuation resulting from adverse events) effects. Similarly, inferiority could be determined via less beneficial (e.g., less efficacy at the primary end point) and/or more harmful (e.g., more discontinuation problems) effects. In cases when a new drug does not appear to offer at least a comparable balance of harms vs. benefits relative to existing treatment alternatives, regulators could consider requiring additional evidence (e.g., a head-to-head randomized, controlled trial) before market approval or could deny market access. For products that offer superiority over placebo but uncertain benefit relative to existing agents on the basis of NMA, conditional approval could be granted while further evidence is gathered from other types of study designs, such as an active comparator trial. This type of adaptive licensing is gaining momentum among regulators [37].

#### 5. Planning for future NMAs

Although the validity of the statistical methods underlying NMA is widely accepted, there is concern about the

combination of direct and indirect evidence post hoc from published data (in a so-called retrospective NMA) [38]. In particular, the potential inconsistency between direct and indirect evidence is a commonly raised criticism [39]. The validity of retrospectively conducted NMA is threatened by publication and reporting biases. Prospective NMA would offer important benefits. A prospective NMA can be defined as a meta-analysis of trials that are identified, evaluated, and determined to be eligible for the meta-analysis before the results of any of those studies are known [40]. Phase 3 trials submitted to regulators for market authorization assessment could form the basis for performing prospective NMA.

The keys to performing prospective NMA are having trials of comparable characteristics with similar patient populations. Regulators could help emphasize the use of similar trial designs and patient populations for different drugs seeking approval for a shared indication in anticipation of future NMA. Whenever possible, trials for a specific indication should conform in terms of patient populations, outcomes, outcome assessment techniques, follow-up time points, and dosing regimens.

Regulatory agency involvement in the design of the trials would help minimize design and population differences among trials, reducing the risk for bias when comparing across trials by ensuring that trials are comparable in terms of relative treatment effect modifiers. Clear communication and regulatory guidance are essential to plan successfully for future NMAs. Similar to current collaborative efforts in determining acceptable surrogate end points and time points for follow-up assessments of randomized trials, manufacturers and regulators could collaborate on predetermining noninferiority and superiority margins when two or more active comparators are evaluated [41]. Reaching consensus a priori on how to evaluate the balance between benefits and harms would be particularly important given the existing challenges in quantifying side effects objectively—which form the basis of regulatory decisions—in relation to clinical effects [42].

Having access to the individual patient-level data from the clinical trials would strengthen considerably the usefulness of NMA. In the case of the FDA, regulatory agency statisticians have access to all individual patient-level data from clinical trials, published or not, which include a large, computerized data set for each clinical study as well as the trial's protocol and clinical study report. Although not required, NMA with individual patient-level data would be desirable when taking into account relative treatment effect modifiers [43]. Using data sources that are, to a great extent, not available to the wider public, regulators can perform their own analyses, assessing the comparability of trials, sources of potential bias, and so forth. Accordingly, regulators could then incorporate NMA results into their decision making and into product labeling, helping to inform the public more completely about new treatments before treatment patterns are established. This not only would

allow for performing comparative assessments at the regulatory level, but also would facilitate downstream after-approval evaluations of drugs by health technology assessment agencies and payers.

## 6. Challenges ahead

Planning future trials to inform future NMAs would go against the current (perceived) practice of planning each individual trial in isolation from others [44]. Although manufacturers may be opposed to designing their trials to mirror those of their competitors, regulators already provide scientific guidance to ensure that separate trials submitted at different time points by different manufacturers are sufficiently comparable clinically to warrant the same indication. Given their current level of involvement, regulators could play a greater role in guiding the design of phase 3 trials to allow future NMAs to be conducted. In an attempt to arrive at a feasible approach, we urge regulators and manufacturers to continue collaborating on issues related to trial design and selection of appropriate comparators, and to ensure that patient populations are as similar as possible across future phase 3 trials in terms of relative treatment effect modifiers.

Moving forward, it may not be possible to design prospectively every aspect of future NMAs. In the case of non-inferiority trials without a placebo arm, there may be a need to use historical evidence from older trials to assess for the assay sensitivity of trials. Certain aspects of our proposal may require legislative action. At the moment, regulators are not required to consider comparative evidence in their market authorization decisions. Although the EMA is favoring increasingly the submission of comparative data for market entry considerations [45], the FDA prefers to consider them on a case-by-case basis [46]. Furthermore, the EMA and the FDA may not be allowed to use proprietary information from the marketing application of one drug in the evaluation of another, which would prevent regulators from performing their own analyses with data sets that are not available to the research community.

Manufacturers may have feasibility concerns about increasing the evidence standards for market entry. As such, it is conceivable that manufacturers may try to circumvent the use of NMA by launching their products in areas with fewer (or weaker) alternatives. However, this challenge extends beyond our proposal and applies to all regulatory evidence standards, particularly in jurisdictions in which off-label use is permitted and commonplace.

## 7. Conclusions

Maximizing the availability of comparative efficacy and safety evidence at the time of market authorization remains critical to maximizing health care value. NMA can be a useful tool to generate comparative evidence at the time of

market authorization assessments. Regulators are positioned uniquely to oversee the design of trials to allow future NMA. During clinical development, regulators and manufacturers should continue to collaborate to choose comparators, determine sample sizes of future trials, and identify relative treatment effect modifiers for future exploration of heterogeneity. NMA can inform approval decisions, may help decrease the likelihood that treatments inferior to existing alternatives are approved, and would help focus downstream comparative effectiveness research efforts by streamlining the information needs of regulators, payers, and health technology assessment agencies.

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