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Statins for primary prevention of venous thromboembolism (Review)

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TABLE OF CONTENTS

[Intervention Review]

Statins for primary prevention of venous thromboembolism

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ABSTRACT

Background

Venous thromboembolism (VTE) is common in clinical practice. The efficacy of statins in the primary prevention of VTE remains unproven. This is an update of the review first published in 2011.

Objectives

To assess the efficacy of statins in the primary prevention of VTE.

Search methods

For this update the Cochrane Peripheral Vascular Diseases (PVD) Group Trials Search Co-ordinator searched the Specialised Register (last searched February 2014) and CENTRAL (2014, Issue 1).

Selection criteria

Randomised controlled trials (RCTs) that assessed statins in the primary prevention of VTE were considered. The outcomes we evaluated were the rates of VTE, cardiovascular and cerebrovascular events, death and adverse events. Two authors (L Li, JH Tian) independently selected RCTs against the inclusion criteria. Disagreements were resolved by discussion with a third author (KH Yang).

Data collection and analysis

Data extraction was independently carried out by two authors (L Li, JH Tian). Disagreements were resolved by discussion with a third author (PZ Zhang). Two authors (L Li, JH Tian) independently assessed the risk of bias according to a standard quality checklist provided by the PVD Group.

Main results

For this update we included one RCT with 17,802 participants that assessed rosuvastatin compared with placebo for the prevention of VTE. The quality of the evidence was moderate because of imprecision, as the required sample size for the outcomes of this review was not achieved. Analysis showed that when compared with placebo rosuvastatin reduced the incidence of VTE (odds ratio (OR) 0.57, 95% confidence interval (CI) 0.37 to 0.86) and deep vein thrombosis (DVT) (OR 0.45, 95% CI 0.25 to 0.79), the risk of any (fatal and non-fatal) myocardial infarction (MI) (OR 0.45, 95% CI 0.30 to 0.69), and any (fatal and non-fatal) stroke (OR 0.51, 95% CI 0.34 to 0.78). There was no difference in the incidence of pulmonary embolism (PE) (OR 0.77, 95% CI 0.41 to 1.46), fatal MI (OR 1.50, 95% CI 0.53 to 4.22), fatal stroke (OR 0.30, 95% CI 0.08 to 1.09) or death after VTE (OR 0.50, 95% CI 0.20 to 1.24). The incidence of any serious adverse events was no different between the rosuvastatin and placebo groups (OR 1.07, 95% CI 0.95 to 1.20).

Authors' conclusions

Available evidence showed that rosuvastatin was associated with a reduced incidence of VTE, but the evidence was limited to a single RCT and any firm conclusions and suggestions could be not drawn. Randomised controlled trials of statins (including rosuvastatin) are needed to evaluate their efficacy in the prevention of VTE.

PLAIN LANGUAGE SUMMARY

Statins for preventing blood clot formation within veins

Background

Venous thrombosis or thromboembolism (VTE) is a condition in which a blood clot (thrombus) forms in a vein and causes a blockage. The blockage most commonly occurs in the 'deep veins' of the lower legs, thighs or pelvis and is called deep vein thrombosis (DVT). If part of or the entire clot breaks away and is carried through the blood (venous) system it is called an embolism. Should the clot reach the lungs, it is known as a pulmonary embolism (PE) and is life threatening. VTE affects about 3,705,000 people worldwide annually and is one of the most preventable causes of hospital deaths. Statins are well known cholesterol-lowering drugs that are used in heart disease. They have other protective effects including anti-clotting properties and may be effective in the prevention of VTE. The objective of this review was to assess the efficacy of statins in the primary prevention of VTE.

Key results

Our review included one published randomised controlled trial, involving 17,802 participants, which reported outcomes of VTE. This trial investigated rosuvastatin compared with placebo for the primary prevention of VTE. Analysis showed that, compared with placebo, rosuvastatin reduced the incidence of VTE and DVT, the risk of any (fatal and non-fatal) myocardial infarction, and any (fatal and non-fatal) stroke. There were no differences between rosuvastatin and placebo in the incidence of pulmonary embolism, fatal myocardial infarction, fatal stroke, and death after VTE. The incidence of any serious adverse events was not different between rosuvastatin and placebo. No firm conclusions or suggestions could be made from these findings. More randomised controlled trials of statins (including rosuvastatin) are needed to evaluate the efficacy of statins in the prevention of VTE.

Quality of the evidence

The quality of the evidence was moderate because of imprecision, as the required sample size for the outcomes of this review was not achieved.

Summary of findings for the main comparison. Statin versus placebo for primary prevention of venous thromboembolism

Statin versus placebo for primary prevention of venous thromboembolism

Patient or population: 17,802 patients with low to normal levels of low density lipoprotein (LDL) cholesterol (< 130 mg/dL)
Settings: 1315 sites in 26 countries on 4 continents, including North and South America, Europe, and Africa
Intervention: rosuvastatin 20 mg daily versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Statin versus placebo				
All cases of VTE Follow-up: median 1.9 years	**Study population**		**OR 0.57** (0.37 to 0.86)	17802 (1 study)	⊕⊕⊕⊖ **moderate** [1]	Figure 1
	7 per 1000	**4 per 1000** (3 to 6)				
	Moderate					
	7 per 1000	**4 per 1000** (3 to 6)				
Pulmonary embolism Follow-up: mean 1.9 years	See comment	See comment	Not estimable	17802 (1 study)	⊕⊕⊕⊖ **moderate** [1]	Appendix 3
Deep vein thrombosis Follow-up: median 1.9 years	See comment	See comment	Not estimable	17802 (1 study)	⊕⊕⊕⊖ **moderate** [1]	Appendix 3
Any MI Follow-up: median 1.9 years	**Study population**		**OR 0.45** (0.3 to 0.69)	17802 (1 study)	⊕⊕⊕⊖ **moderate** [1]	Appendix 3
	8 per 1000	**3 per 1000** (2 to 5)				
	Moderate					
	8 per 1000	**4 per 1000** (2 to 6)				
Any stroke	**Study population**		**OR 0.51**	17802	⊕⊕⊕⊖	Appendix 3

Follow-up: median 1.9 years	**7 per 1000**	**4 per 1000** (2 to 6)	(0.34 to 0.78)	(1 study)	**moderate** [1]	
	Moderate					
	7 per 1000	**4 per 1000** (2 to 5)				
Death Follow-up: median 1.9 years	**Study population**		**OR 0.8** (0.66 to 0.96)	17802 (1 study)	⊕⊕⊕⊖ **moderate** [1]	Appendix 3
	28 per 1000	**22 per 1000** (18 to 27)				
	Moderate					
	28 per 1000	**23 per 1000** (19 to 27)				
Any serious adverse event Follow-up: median 1.9 years	**Study population**		**OR 1.07** (0.95 to 1.2)	17802 (1 study)	⊕⊕⊕⊖ **moderate** [1]	Appendix 3
	66 per 1000	**70 per 1000** (63 to 78)				
	Moderate					
	66 per 1000	**70 per 1000** (63 to 78)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Total sample size is lower than the calculated optimal information size (OIS). Therefore the evidence was downgraded based on imprecision

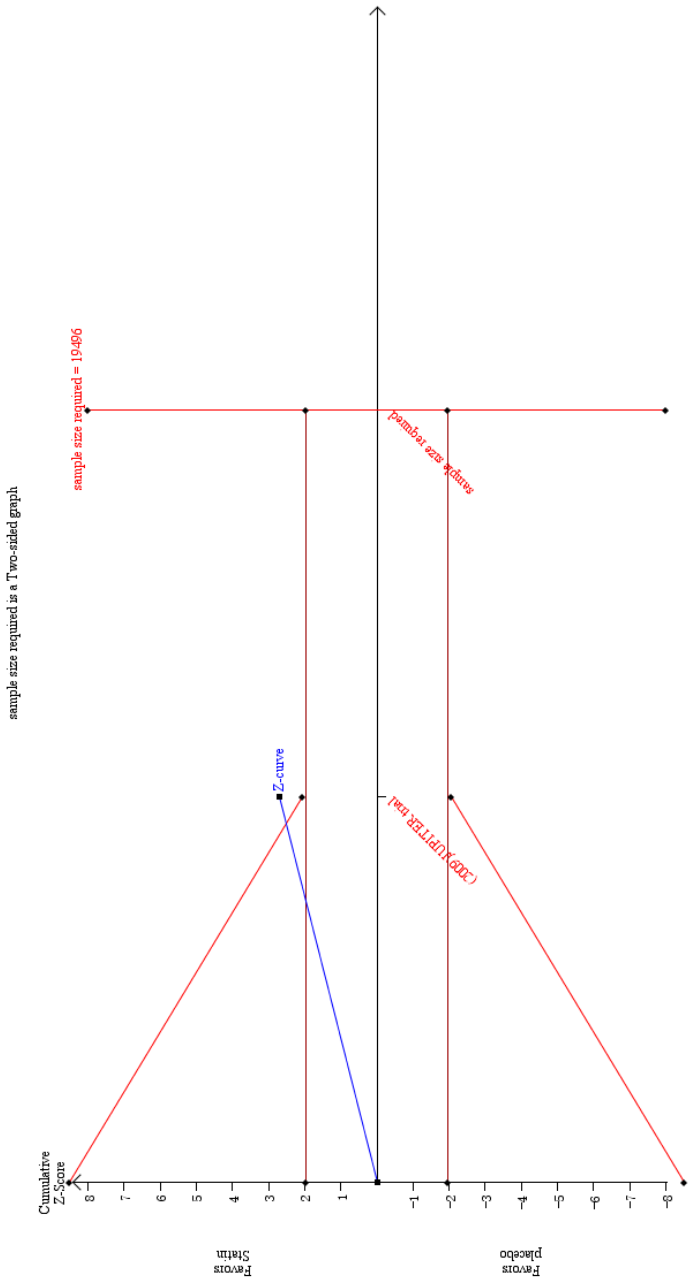


Figure 1. Trial sequential analysis results for the incidence of VTE.

BACKGROUND

Description of the condition

Venous thromboembolism (VTE) is a clinical entity which has two different manifestations, deep venous thrombosis and pulmonary embolism. Venous thrombosis is a condition in which a blood clot (thrombus) forms in an intact vein as red blood cells, fibrin and, to a lesser extent, platelets and leucocytes (white blood cells) form a mass. Blood flow through the affected vein is limited by the clot, causing swelling and pain. Venous thrombosis most commonly occurs in the 'deep veins' in the lower legs, thighs, or pelvis, so it is usually called deep vein thrombosis (DVT). An embolism is created if a part or all of the blood clot breaks off from the site where it is created and travels through the venous system. If the clot lodges in the lungs a very serious condition arises, pulmonary embolism (PE).

The crude annual incidence per 1000 population is 0.83 for VTE, 0.52 for DVT, and 0.31 for PE. The annual incidence per 1000 population after age adjustment to the World Health Organization World Standard Population is 0.57 for VTE, 0.35 for DVT, and 0.21 for PE. If the crude annual incidence of VTE is externally valid, then VTE affects about 17,000 Australians and 3,705,000 people all over the world annually (calculated as 65,000 million all over) (Ho 2008; Raju 2009). Retrospective studies reported mortality rates following VTE of 5% to 23% (Goldhaber 2004), although in symptomatic patients with adequate anticoagulation mortality was 1% to 2% (Douketis 1998). It was estimated that more than 900,000 Americans develop DVT each year, and 500,000 of these develop PE with 30% of PEs being fatal (Heit 2005). About two-thirds of all VTE events were related to hospitalisation. Heit et al reported that VTE is the third most common cause of hospital-related deaths in the United States and the most common preventable cause of hospital deaths (Heit 2002).

Thrombosis prophylaxis can be achieved by physical or pharmacological means. The decision on which prophylaxis is used depends on patient risk factors, the availability of recommended medication, and the clinical judgment of the treating doctor (Chapman 2009). The most effective anticoagulants (recommended for prophylaxis in the highest risk patients) are the low molecular weight heparins and fondaparinux (Alpert 2001; Diuguid 2001). Mechanical prophylaxis (that is intermittent pneumatic compression stockings or graduated compression stockings) is recommended for patients with a higher than normal risk of bleeding or as an adjunct to more efficacious pharmacological prophylaxis (Chapman 2009; Diuguid 2001).

Description of the intervention

Statins are 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase inhibitors and they are the most powerful cholesterol-lowering drugs available. They have also been shown to exhibit several vascular protective effects, with antithrombotic properties (Undas 2005). As a result, the benefits of statins might accrue not only from their effects on lipid levels but also through their influence on thrombosis and inflammation (Albert 2001; Kaba 2004; Undas 2005).

The Heart and Estrogen/Progestin Replacement Study (HERS), a randomised trial of postmenopausal hormone therapy in American women with cardiovascular disease, first observed a lower risk of VTE in women using statins (Grady 2000). In this trial of 2763 women there were nearly 1000 women using statins and the relative risk (RR) of VTE was 0.5. In a study of administrative data, Ray reported that statins users in Ontario had a 22% lower risk of VTE than those prescribed thyroid replacement therapy (Ray 2001a). An analysis by Yang of the General Practice Research Database (GPRD) in the UK was not able to detect an association between statins use, or other lipid-lowering drug use, and the risk of unprovoked VTE, but the study was limited by the analysis of a small number of cases (Yang 2002). Huerta also examined GPRD data using a longer time period and assessing over 6550 cases, and reported a 15% lower risk of VTE with the use of statins although this was not statistically significant (odds ratio (OR) 0.85) (Huerta 2007). In a study by Ramcharan 2009 of 4538 patients who had previously experienced a single episode of DVT or PE and 5914 control patients, 3.3% of participants using statins experienced a VTE as compared with 5.7% of controls, which yielded a 59% lower risk of VTE with statins use. This association was not seen with other lipid-lowering medications, which were not associated with a lower, or higher, risk of VTE. Two prospective observational studies showed that substantial and significant reductions in the risk of VTE were associated with the use of statins, a 50% reduction in the risk among statin users in the HERS (Grady 2000) and a 22% reduction among statin users in Ontario, Canada as calculated on the basis of administrative claims data (Ray 2001a). Four case-control studies also showed reductions in the risk of venous thrombosis, ranging from 26% to 58%, associated with the use of statins (Doggen 2004; Lacut 2004; Lacut 2008; Ramcharan 2009; Sørensen 2009) (Table 1).

However, some people think that statins cannot be recommended for use in either the prevention or the treatment of VTE, and that research studies should attempt to quantify the risk reduction for VTE with statin use (Ray 2001b). We intended to clarify the efficacy and safety of statins in this review.

How the intervention might work

Plausible biological links can be found between statin therapy and reduction of thrombotic risk, mainly targeting the immune system, blood coagulation, endothelium, lipid metabolism and inflammation (Lippi 2013). Statins can exhibit antithrombotic properties that are not associated with changes in lipid profile. Increasing evidence indicates that statins modulate the blood coagulation cascade at multiple levels, leading to reduced thrombogenicity (Undas 2005). Statins inhibit platelet aggregation and maintain a favourable balance between prothrombotic and fibrinolytic mechanisms (Ray 2003b). Differences between individual statin medications may be due to differences in metabolism (Corsini 1999). For example, simvastatin impairs the activation of prothrombin, factor V (FV) and FXIII, and enhances FVa inactivation by activated protein C (Undas 2001), which may lead to a reduced risk of venous thrombosis. A recent systematic review showed that statin therapy reduces interleukin 6 (IL-6) induced expression of C-reactive protein (CRP) and monocyte chemoattractant protein-1 (MCP-1), which has been linked to vein wall fibrosis, promoting post-thrombotic syndrome (PTS) and recurrent DVT in patients (Rodriguez 2012). Meanwhile, this review suggests that the anti-thrombotic effects are likely to be exhibited through the anti-inflammatory properties of statins (Rodriguez 2012).

Why it is important to do this review

The optimal drug in the primary prevention of VTE is one that is efficacious, associated with minimal bleeding risk, and easy to administer. Statins fulfil the latter two criteria, but their efficacy and side effects remain unproven (Ray 2003b). In this review we wanted to assess their efficacy and safety by evaluating randomised controlled trials (RCTs) using statins for the primary prevention of VTE.

OBJECTIVES

To assess the efficacy of statins in the primary prevention of venous thromboembolism (VTE).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were considered, without language and publication status restrictions.

In this review, only primary prevention trials were included. We used the primary prevention definition provided in the US Preventive Services Task Force Guide to Clinical Preventive Services (USPSTF): to provide primary prevention measures to individuals to prevent the onset of a targeted condition. Primary prevention measures include activities that help avoid a given healthcare problem.

We excluded studies if they did not assess the primary outcome of this review, the rate of VTE (DVT and PE), as an outcome in the study. The primary outcome of the review could be assessed as either a primary, secondary or exploratory outcome of the study.

Types of participants

Participants were healthy people, patients with diseases other than VTE, or people with risk factors (see Appendix 1).

Types of interventions

We included all types of statin treatment as compared to all types of control interventions, including placebo.

Types of outcome measures

Primary outcomes

- The rate of VTE (DVT and PE)

VTE is detected by imaging using venous ultrasonography or venography for confirmation of DVT, and angiography, computed tomography (CT) or a ventilation and perfusion scan (V/Q) for confirmation of PE; or any other recognised confirmatory tests for either DVT or PE. VTE was also divided into unprovoked and provoked venous thrombosis. Unprovoked venous thrombosis was defined as occurring in the absence of known malignancy (diagnosed either before or up to three months after the venous thrombosis), trauma, hospitalisation or surgery within the three months before the event. Provoked venous thrombosis included events that occurred in patients with cancer or during, or shortly after, trauma, hospitalisation or surgery.

Secondary outcomes

- The rate of cardiovascular and cerebrovascular events (myocardial infarction (MI), stroke, arterial revascularisation, etc.)
- The rate of death (all deaths, death after VTE)
- Adverse events:
  a. adverse events (myopathy, tendon manifestations, etc.);
  b. serious adverse events (SAEs).

SAEs were any adverse events that resulted in any of the following outcomes: death, a life threatening adverse event, inpatient hospitalisation or prolongation of existing hospitalisation, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life threatening, or require hospitalisation may be considered as serious.

Search methods for identification of studies

There were no language or publication status restrictions.

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched February 2014) and the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 1), part of *The Cochrane Library* (www.thecochranelibrary.com). See Appendix 2 for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.thecochranelibrary.com).

Searching other resources

In addition, we searched the reference lists of retrieved articles and other related literature reviews.

Data collection and analysis

Selection of studies

We used the search strategies described to obtain titles and abstracts of studies that were potentially relevant to the review. Two authors (L Li, JH Tian) independently selected RCTs of statins in the prevention of VTE by screening titles and abstracts against the predetermined eligibility criteria to discard studies that were not applicable.

If we could not decide whether the articles satisfied the inclusion criteria from the abstracts, the full texts of the trials were obtained. If there were two or more publications relating to one trial, only the publication with the most complete data or the pooled data from all the publications was included. Disagreements were resolved by discussion with a third author (KH Yang).

Data extraction and management

Data extraction was independently carried out by the same two authors (L Li, JH Tian) and the results were checked for accuracy

by a third author (PZ Zhang). Disagreements were resolved by discussion. A paper data extraction form provided by the Peripheral Vascular Diseases (PVD) Group was used to record the following characteristics:

- title;
- authors;
- publication status (if published, which journal, year of publication, the volume, the issue and the pages; if not published, year in which study was conducted and other relevant details);
- study design;
- blinding;
- method of randomisation;
- method of concealment of allocation;
- exclusions post-randomisation;
- losses to follow-up;
- intention-to-treat analysis;
- country;
- setting or location of trial;
- type of participants;
- risk factors of participants;
- number of participants;
- number of participants allocated to each type of intervention;
- stated inclusion and exclusion criteria;
- age of participants;
- sex of participants;
- doses and routes of administration;
- duration of the follow-up;
- type of VTE;
- primary and secondary outcomes;
- references to relevant studies.

Assessment of risk of bias in included studies

To avoid bias, we assessed the methodological quality of each trial according to a standard quality checklist provided by the PVD Group. Two authors (L Li, JH Tian) independently assessed the risk of bias of each trial as described below, recorded the information in a table, and provided a narrative description in the text. If there was insufficient information about the study methods, we contacted the authors for further information. If the trial authors did not respond within four or more weeks, we assessed the risk of bias from the available information. Disagreements were resolved by consensus. The following items were assessed as 'low risk' (low risk of bias), 'unclear risk' (uncertain risk of bias), or 'high risk' (high risk of bias).

A. The selection bias was evaluated based on the randomisation procedure and allocation concealment

1) Randomisation method

Low risk (low risk of bias): the method allowed participants of studies to have the same chance of receiving each intervention and the investigators described a random component in the sequence generation process, such as referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots.

High risk (high risk of bias): the investigators described a non-random component in the sequence generation process. Usually the description involved some systematic, non-random approach, such as by odd or even date of birth, some rule based on date (or day) of admission, hospital or clinic record number. Other non-random approaches are used much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgment or some method of non-random categorisation of participants, such as allocation by the judgment of the clinician, preference of the participant, the results of a laboratory test or a series of tests, or availability of the intervention. If an open random allocation schedule (for example a list of random numbers) was used or assignment envelopes were used without appropriate safeguards (for example if envelopes were unsealed or non-opaque, or not sequentially numbered), or any other explicitly unconcealed procedure, we classified the randomisation method as at 'high risk of bias'.

Unclear risk: insufficient information was available about the sequence generation process to permit judgment of 'low risk' or 'high risk', for example insufficient information about the randomisation procedure, such as randomisation stated but no information given on the method used.

2) Allocation concealment

Low risk (low risk of bias): if the randomisation method that was described would not allow investigators or participants to know or influence the intervention group before eligible participants entered into the study (for example central allocation, including telephone, web-based and pharmacy-controlled randomisation; sequentially-numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).

High risk (high risk of bias): if an open random allocation schedule (for example a list of random numbers) was used, assignment envelopes were used without appropriate safeguards (for example if envelopes were unsealed or non-opaque, or not sequentially numbered), by alternation or rotation, date of birth or case record number, or any other explicitly unconcealed procedure.

Unclear risk: insufficient information about allocation concealment, such as allocation concealment stated but no information available on the method used, or the authors did not report on allocation.

The randomisation procedure and allocation schedule are usually impossible to achieve low risk of bias in for quasi-randomised controlled trials (QRCTs), so we evaluated these as 'high risk of bias'.

B. We evaluated performance bias based on blinding of patients and people administering the treatment

Low risk (low risk of bias): the study described methods of blinding patients and people administering the treatment that were appropriate, so that participants and people administering the treatment did not know the exact treatment for each group until the blinding was broken; either participants or some key study personnel were not blinded but outcome assessment was blinded and the non-blinding of others was unlikely to introduce bias.

High risk (high risk of bias): no blinding was used for the participants and people administering the treatment.

Unclear risk: insufficient information to permit judgment of 'low risk' or 'high risk', or no useful information obtained from the authors.

C. Attrition bias was assessed by looking at the follow-up to see if at least 80% of participants in all groups were included in the final analysis and an intention-to-treat analysis was used

Low risk (low risk of bias): < 20% of participants withdrawn or lost to follow-up because of side effects of treatment or other reasons, and also the reasons for why participants were lost and withdrawn were stated. Intention-to-treat analysis was specifically reported.

High risk (high risk of bias): > 20% of participants withdrawn or lost to follow-up because of side effects of treatment or other reasons, and also the reasons why lost and withdrawn were not stated. Intention-to-treat analysis was not used if there were participants withdrawn or lost to follow-up.

Unclear risk: the losses to follow-up were not reported or could not be judged from the article.

D. Detection bias was assessed by evaluating the method of outcome assessment or blinding of outcome assessor

Low risk (low risk of bias): same methods of ascertainment for both groups and blinding of outcome assessor for assessing the outcomes.

High risk (high risk of bias): different methods of ascertainment for both groups, or non-blinding of outcome assessor for assessing the outcomes.

Unclear risk: methods of ascertainment for both groups and blinding of outcome assessor for assessing the outcomes were not reported.

E. Other biases were evaluated based on incomplete outcome data and selective outcome reporting

1) Incomplete outcome data

Low risk (low risk of bias): no missing outcome data; missing outcome data balanced between groups with similar reasons and numbers lost for the missing data across groups; missing outcomes not enough to have a clinically relevant impact on the final results; missing data have been imputed using appropriate methods.

High risk (high risk of bias): reason for missing outcome data related to true outcome, with either imbalance in numbers or reasons across the groups; missing outcomes enough to induce clinically relevant bias in the results; inappropriate methods were used to deal with the missing data.

Unclear risk: cannot judge from the information obtained from the article.

2) Selective outcome reporting

Low risk (low risk of bias): all the study's pre-specified (primary and secondary) outcomes were reported in the article (if the study protocol was available) or all expected outcomes were mentioned in the published reports (the study protocol was not available).

High risk (high risk of bias): one or more of the study's pre-specified primary or expected outcomes failed to be included or was not reported.

Unclear risk: there was insufficient information to judge 'low risk' or 'high risk'.

Measures of treatment effect

According to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we defined measures of treatment effects as follows. For dichotomous outcomes, we expressed results as odds ratio (OR) with 95% confidence interval (CI). If there were continuous scales of measurement to assess the effects of treatment, we used the mean difference (MD), or the standardised mean difference (SMD) if different scales were used. We analysed heterogeneity using the I^2 statistic based on N - 1 degrees of freedom with an alpha of 0.05 for statistical significance (Higgins 2011).

Unit of analysis issues

Individual participants were the unit of analysis because we intended to include individually randomised controlled trials with a parallel design.

Dealing with missing data

We attempted to contact all the authors (if e-mails, telephone numbers, or fax details were available) of the original studies for the missing data. If the authors of the study did not respond within four or more weeks, we extracted all the available data from the publication. If data were missing because of dropping out of participants or losses to follow-up, we planned to conduct a primary analysis based on the provided data and a sensitivity analysis with missing data imputed based on the worst-case and best-case scenarios.

Assessment of heterogeneity

We examined heterogeneity among trials using the I^2 statistic. An I^2 statistic estimate greater than 50% was considered as substantial or considerable heterogeneity. Its causes were investigated by performing subgroup analyses, or sensitivity analyses by excluding studies thought to cause the heterogeneity.

Assessment of reporting biases

If possible, we planned to assess reporting biases by using funnel plots.

Data synthesis

We used the software (RevMan 5) provided by The Cochrane Collaboration for statistical analysis, based on an intention-to-treat analysis. We considered meta-analysis to determine the appropriate measure of effect if the search yielded a group of trials sufficiently homogeneous in terms of measured outcomes. According to the level of heterogeneity between trials, we used either a fixed-effect or random-effects model where appropriate. We pooled the outcomes and examined the differences between the two models. We planned to report the results qualitatively if we found significant heterogeneity and we could not find the reasons for the heterogeneity.

Trial sequential analysis

Meta-analyses may result in type 1 errors due to sparse data and repeated significance testing when meta-analyses are updated with new trials (Brok 2008). Trial sequential monitoring boundaries

were determined using trial sequential analysis (TSA) software (Thorlund 2011). If the cumulative Z-curve crosses a trial sequential monitoring boundary (TSMB), a sufficient level of evidence is reached and no further trials may be needed. However, there is insufficient evidence to reach a conclusion if the cumulative Z-curve does not cross the TSMB or does not surpass the futility boundaries before the required information size is reached (Bjelakovic 2014). We also calculated a required information size, which is the least number of participants in a meta analysis to detect or reject a certain intervention effect, and adjusted the required information size to account for statistical between-trial heterogeneity with a diversity adjustment factor (Wetterslev 2009). In our meta-analysis, the diversity-adjusted required information size was based on the event proportion in the control group; the assumption of a plausible RR reduction of 20%; a risk of type I error of 5%; a risk of type II error of 20%; and the assumed diversity of the meta-analysis (Wetterslev 2009).

Subgroup analysis and investigation of heterogeneity

We intended to undertake relevant subgroup analyses of the review data. We conducted subgroup analysis for different ages, gender and population (healthy people versus people considered to be at risk).

Sensitivity analysis

We used sensitivity analysis to explore the impact of missing data or different studies on the stability of the treatment effect.

Summary of findings table

We employed the GRADE approach to interpret findings (Guyatt 2008), and the GRADE profiler (GRADEPRO) allowed us to import data from Review Manager 5.3 to create a summary of findings table. This table provides outcome-specific information concerning the overall quality of evidence from studies included in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes that we considered, given our trial sequential analyses (Bjelakovic 2014). The following outcomes were included in the summary of findings table: all VTE, PE, DVT, MI, stroke, death and serious adverse events.

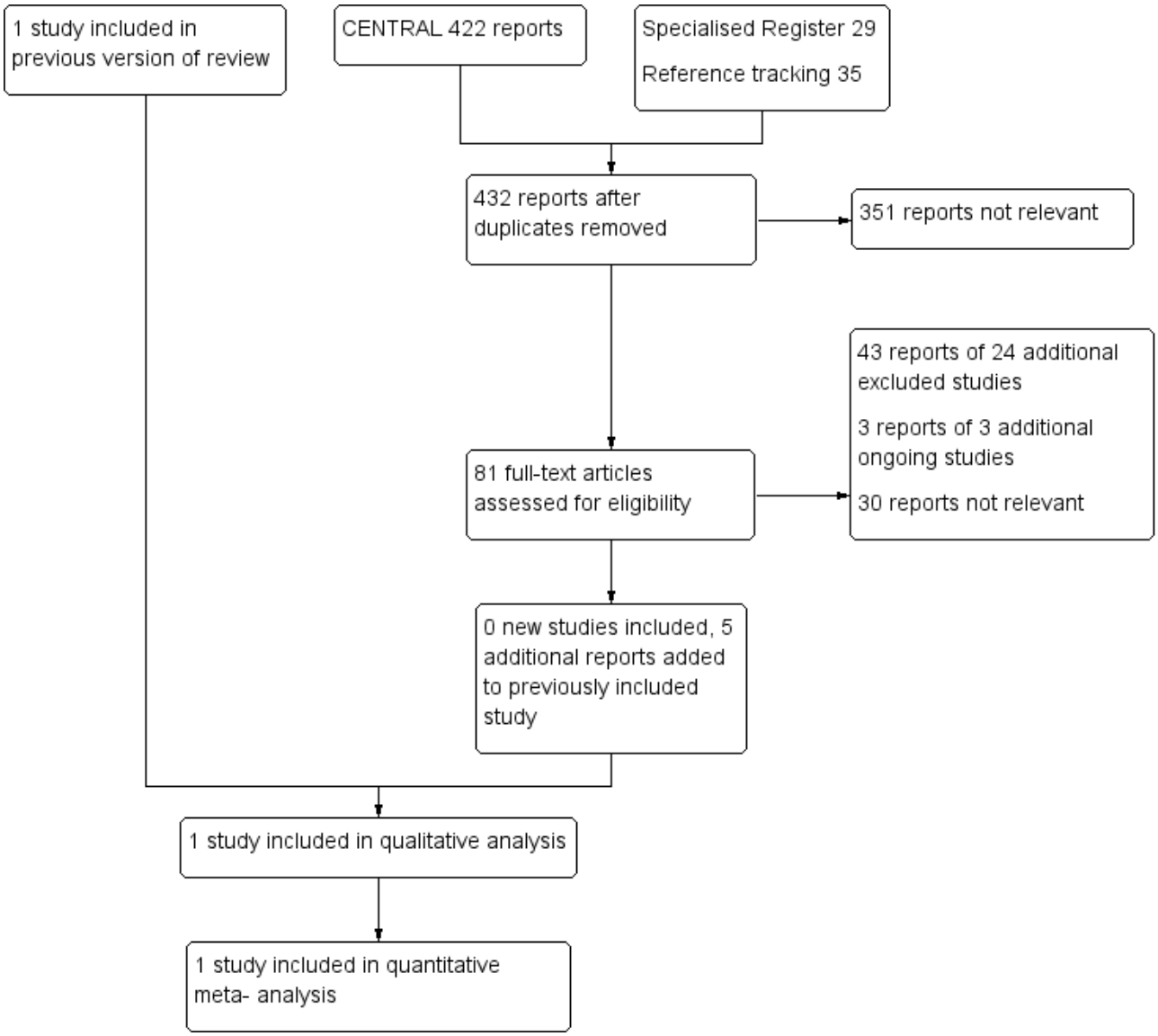
RESULTS

Description of studies

Results of the search

See Figure 2 for details of the search results.

Figure 2. Study flow diagram.



Included studies

See Characteristics of included studies.

No additional studies were included in this update. There is one included study (JUPITER trial), which investigated rosuvastatin. This study used rosuvastatin 20 mg daily for healthy people aged 50 years and older without a history of cardiovascular or cerebrovascular events. Characteristics of the included study are presented in the Characteristics of included studies table.

Excluded studies

See Characteristics of excluded studies.

For this update there were 24 additional studies excluded (ACCEPT-D; AFCAPS/TexCAPS; AIM-HIGH; ASTRONOMER; Caramelli 2002; CARDS; ChiCTR-TNRC-08000263; DECREASE III; ELIMIT; Ge 2011; Haak 2001; HPS2-THRIVE; Jeong 2013; LEADe; Liu 2011; MEGA; METEOR; PROCEDURE; PROSPER; RATIONAL; Rosen 2013; Shai 2014; van der Loo 2011; West 2010). This made a total of 36 excluded studies (ACCEPT-D; AFCAPS/TexCAPS; AIM-HIGH; ASTRONOMER; Caramelli 2002; CARDS; ChiCTR-TNRC-08000263; DECREASE III; Doggen 2004; ELIMIT; Ge 2011; Haak 2001; HERS; HPS2-THRIVE; Huerta 2007; Jeong 2013; Lacut 2004; Lacut 2008; LEADe; Liu 2011; MEGA; METEOR; NCT00437892; PROCEDURE; PROSPER; Ramcharan 2009; RATIONAL; Ray 2001a; Rosen 2013; Shai 2014; Smeeth 2009; Stangier 2009; Sørensen 2009; van der Loo 2011; West 2010; Yang 2002). Four reports which had previously been excluded were assessed as not relevant in this update.

Eight of the excluded studies were case-control studies (Doggen 2004; Huerta 2007; Lacut 2004; Lacut 2008; PROSPER; Ramcharan 2009; Shai 2014; Sørensen 2009); five were cohort studies (ChiCTR-TNRC-08000263; HERS; Ray 2001a; Smeeth 2009; Yang 2002); 17 were not VTE primary prevention studies (ASTRONOMER; Caramelli 2002; CARDS; DECREASE III; ELIMIT; Ge 2011; Haak 2001; Jeong 2013; Liu 2011; MEGA; METEOR; PROCEDURE; RATIONAL; Rosen 2013; Stangier 2009; van der Loo 2011; NCT00437892); and six

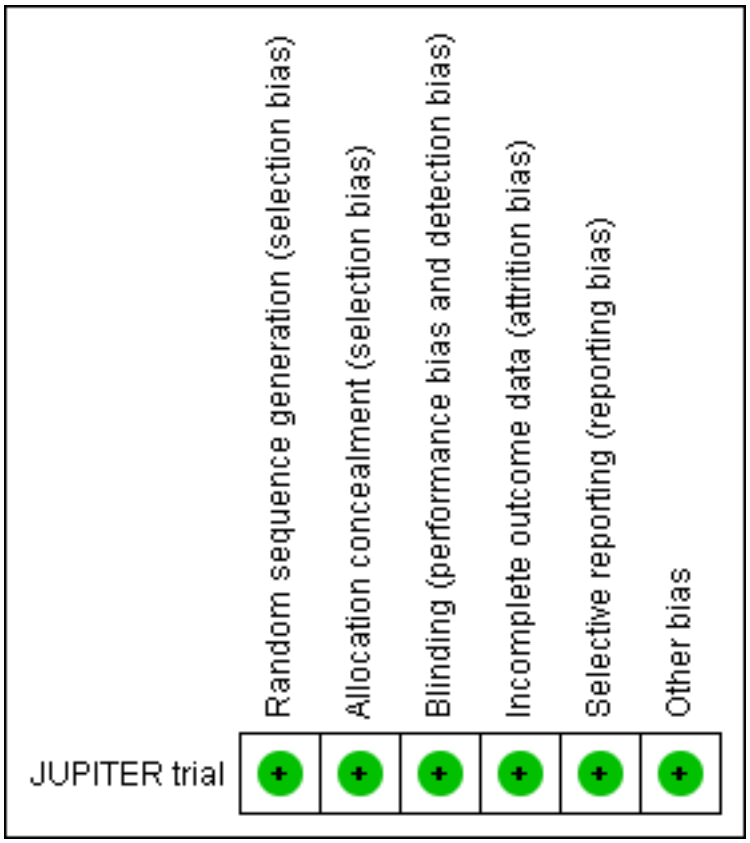
studies focused on both statins and other interventions (ACCEPT-D; AFCAPS/TexCAPS; AIM-HIGH; HPS2-THRIVE; LEADe; West 2010).

For this update there were three additional ongoing studies (NCT00259662; NCT01063426; NCT01524653), making a total of four ongoing studies (NCT00259662; NCT01021488; NCT01063426; NCT01524653).

Risk of bias in included studies

The risk of bias assessment for the included study is presented in Characteristics of included studies and Figure 3.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The method of randomisation was on the basis of a computer generated list. Randomisation was performed with the use of an interactive voice-response system and was stratified according to centre (JUPITER trial).

Blinding

A closeout visit occurred after study termination, at which time participants were unblinded. All reported primary endpoints were adjudicated by an independent endpoint committee blinded to the randomised treatment assignment. Adverse events were monitored and reported in a blinded manner until the date of the closeout visit and discontinuation of therapy (JUPITER trial).

Incomplete outcome data

We compared the study protocol and study publications and found no missed reporting of outcomes. Therefore, there were no incomplete outcome data in this included study.

Selective reporting

We compared the study protocol and the study and we found that all pre-specified outcomes were reported in the relevant publications. Therefore, there was no selective reporting in this included study.

Other potential sources of bias

The trial was financially supported by AstraZeneca. The authors of all publications reported that the sponsor collected the trial data and monitored the study sites but played no role in the conduct of the analyses or drafting of the manuscript (JUPITER trial). Therefore, funding should not have introduced potential biases in this trial.

Effects of interventions

See: **Summary of findings for the main comparison** Statin versus placebo for primary prevention of venous thromboembolism

As outlined in the protocol, we have presented the results for dichotomous outcomes using ORs with 95% CIs and for continuous

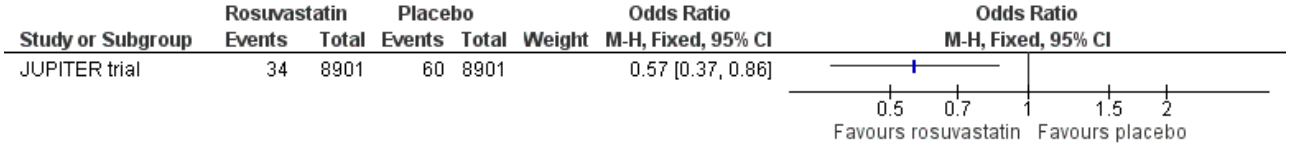
outcomes using the mean difference (MD) with 95% CI, or the standardised mean difference (SMD) if different scales were used.

The rates of VTE

Symptomatic PE or DVT occurred in 94 participants during a median follow-up time of 1.9 years. The rates of VTE were 0.18 and 0.32 events per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio (HR) 0.57, 95% CI 0.37 to 0.86; P = 0.007).

Our analysis showed that, compared with placebo, rosuvastatin could reduce the incidence of all cases of VTE (rosuvastatin 34/8901, placebo 60/8901; OR 0.57, 95% CI 0.37 to 0.86) (Analysis 1.1, Figure 4), provoked VTE (rosuvastatin 15/8901, placebo 29/8901; OR 0.52, 95% CI 0.28 to 0.96) (Analysis 1.2), and DVT only (rosuvastatin 17/8901, placebo 38/8901; OR 0.45, 95% CI 0.25 to 0.79) (Analysis 1.3). There was no difference between rosuvastatin and placebo in the incidence of unprovoked VTE (rosuvastatin 19/8901, placebo 31/8901; OR 0.61, 95% CI 0.35 to 1.08) (Analysis 1.4) and PE (rosuvastatin 17/8901, placebo 22/8901; OR 0.77, 95% CI 0.41 to 1.46) (Analysis 1.5).

Figure 4. Forest plot of comparison: 1 Rosuvastatin versus placebo, outcome: 1.1 All cases of VTE.



We found that, compared with placebo, rosuvastatin could reduce the incidence of all VTE in men (OR 0.50, 95% CI 0.30 to 0.84) (Analysis 1.6) and patients aged 50 to 69 years (OR 0.55, 95% CI 0.31 to 0.96) (Analysis 1.7) but there was no difference between rosuvastatin and placebo in the incidence of all VTE in women (OR 0.74, 95% CI 0.35 to 1.56) (Analysis 1.6) and patients aged 70 to 97 years (OR 0.59, 95% CI 0.31 to 1.11) (Analysis 1.7).

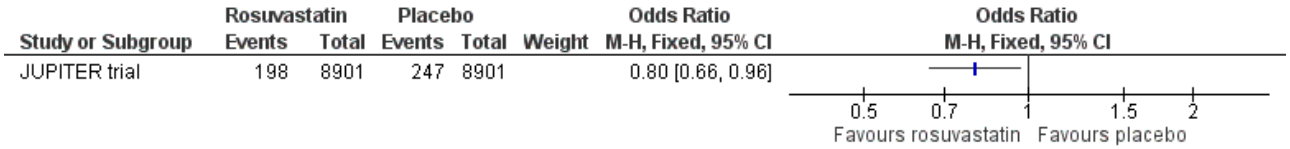
The rates of cardiovascular and cerebrovascular events

From our analysis, we found that, compared with placebo, rosuvastatin could reduce the risk of cardiovascular events in a healthy population (OR 0.71, 95% CI 0.57 to 0.89) (Analysis 1.8), any MI (OR 0.45, 95% CI 0.30 to 0.69) (Analysis 1.9), any stroke (OR 0.51, 95% CI 0.34 to 0.78) (Analysis 1.11) and arterial revascularisation (OR 0.54, 95% CI 0.40 to 0.72) (Analysis 1.13). There was no difference between rosuvastatin and placebo in fatal MI (OR 1.50, 95% CI 0.53 to 4.22) (Analysis 1.10) and fatal stroke (OR 0.30, 95% CI 0.08 to 1.09) (Analysis 1.12).

The rates of death

Rosuvastatin could reduce the incidence of any death (OR 0.80, 95% CI 0.66 to 0.96) (Analysis 1.14, Figure 5) but there was no difference between rosuvastatin and placebo in the incidence of death after VTE (OR 0.50, 95% CI 0.20 to 1.24) (Analysis 1.15) or death resulting from cardiovascular causes (OR 0.76, 95% CI 0.42 to 1.38) (Analysis 1.16).

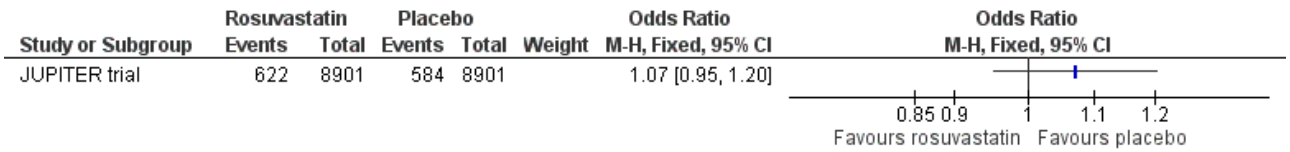
Figure 5. Forest plot of comparison: 1 Statin versus placebo, outcome: 1.14 Death.



Adverse events

There was no difference between rosuvastatin and placebo in the incidence of any serious adverse event (OR 1.07, 95% CI 0.95 to 1.20) (Analysis 1.17, Figure 6). Similar results were reported in hepatic disorder (OR 1.17, 95% CI 0.96 to 1.42) (Analysis 1.18); myopathy (OR 1.11, 95% CI 0.45 to 2.74) (Analysis 1.19); rhabdomyolysis (OR 3.00, 95% CI 0.12 to 73.66) (Analysis 1.20); renal disorder (OR 1.12, 95% CI 0.99 to 1.27) (Analysis 1.21); bleeding (OR 0.94, 95% CI 0.79 to 1.11) (Analysis 1.22); muscular weakness, stiffness or pain (OR 1.04, 95% CI 0.96 to 1.13) (Analysis 1.23); or gastrointestinal disorder (OR 1.03, 95% CI 0.96 to 1.11) (Analysis 1.24).

Figure 6. Forest plot of comparison: 1 Rosuvastatin versus placebo, outcome: 1.17 Any serious adverse event.



Trial sequential analysis (TSA)

Figure 1 showed the trial sequential analysis (TSA) results for the main outcome: the incidence of VTE. The cumulative Z-curve crossed the trial sequential monitoring boundaries and the required information size was not reached. This suggests that evidence was sufficient, although the sample size was not large enough. TSA results for the remaining outcomes in the Summary of findings for the main comparison are described in Appendix 3.

Summary of findings

A summary of the results is presented in Summary of findings for the main comparison.

DISCUSSION

Summary of main results

Even though there are other statins that can be used for preventing VTE (Doggen 2004; HERS; Huerta 2007; Lacut 2004; Lacut 2008; Ramcharan 2009; Ray 2001a; Smeeth 2009; Sørensen 2009; Yang 2002), due to of a lack of RCTs evaluating the effects of statins in the primary prevention of VTE we only included one RCT of rosuvastatin (JUPITER trial) in this systematic review.

Our analysis showed that, compared with placebo, rosuvastatin could reduce the incidence of all cases of VTE and provoked VTE and DVT, but there was no difference between rosuvastatin and placebo in the incidence of unprovoked VTE or PE. We found that rosuvastatin could reduce the incidence of all VTE in men and patients aged 50 to 69 years but there was no difference between rosuvastatin and placebo in the incidence of all VTE in women or patients aged 70 to 97 years. Rosuvastatin could reduce the risk of any MI, any stroke, arterial revascularisation, and cardiovascular events, but there was no difference between rosuvastatin and placebo in the risk of fatal MI and fatal stroke. The incidence of any death was reduced with rosuvastatin but there was no difference between rosuvastatin and placebo in the incidence of death after VTE and confirmed deaths resulting from cardiovascular events. There was no difference between rosuvastatin and placebo in the incidence of any serious adverse events. Similar results were reported for adverse effects including bleeding, muscular weakness, stiffness or pain, myopathy, rhabdomyolysis, gastrointestinal disorders, renal disorders and hepatic disorders.

Overall completeness and applicability of evidence

Only one RCT that included 17,802 healthy participants assessed the efficacy of statins for the prevention of VTE. After subgroup analysis, it appears that some participants with risk factors for VTE could benefit from rosuvastatin treatment, but the results of this study might not apply to patients with risk factors which were not investigated by this trial. In addition, this trial was stopped early on the advice of the independent data and safety monitoring board, after a median follow-up of less than two years, based on the size and precision of the observed treatment benefit as well as effects on the rates of death in patients treated with rosuvastatin compared with placebo. As a result, the effects of longer-term therapy cannot be ascertained. Rosuvastatin was not associated with adverse events such as bleeding, muscular weakness, stiffness or pain, or gastrointestinal disorders. Such adverse events are of importance to patients and these adverse events might force patients to stop taking rosuvastatin. Therefore, even though rosuvastatin showed exciting beneficial effects for preventing VTE in some patient groups, there are limitations to applying the results to other patient groups.

Even though all the data from this review came from just one study, the participants were from 26 countries worldwide. However there were very few participants in some countries, for example Uruguay, Switzerland, Romania and Chile. Most of the participants were from Canada, South Africa, United Kingdom and the United States. As a result, the results represented only a part of the world.

A recent systematic review (Rodriguez 2012) showed that statin therapy reduces IL-6 induced expression of CRP and MCP-1, which has been linked to vein wall fibrosis, promoting post-thrombotic syndrome (PTS) and recurrent DVT in patients. This could explain why statins may reduce the incidence of VTE, but the available evidence about statins in the primary prevention of VTE is limited. Due to insufficient evidence, we could not conclude that statin use can reduce the incidence of VTE. However, based on the JUPITER trial, statin use by the general healthy population may reduce the risk of VTE.

Quality of the evidence

The one included study is a randomised, double-blind, placebo-controlled trial which used a computer to generate the randomisation sequence; the random allocation sequence was implemented with the use of an interactive voice-response system. All the primary endpoints that were evaluated were adjudicated by an independent endpoint committee blinded to the randomised treatment assignment. We compared the study protocol and study publications and found no missing outcomes or selective reporting. Even though the trial was financially supported by AstraZeneca, the authors of all publications reported that the sponsor collected the trial data and monitored the study sites but played no role in the conduct of the analyses or drafting of the manuscripts. As a result, funding should not have introduced biases in this trial. In addition, there was no indirectness of evidence (indirect population, intervention, control, outcomes) (Higgins 2011), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses) (Higgins 2011), or high probability of publication bias in this study. The very few limitations in the design and implementation of the study therefore suggest a low likelihood of bias. However, for all outcomes in the Summary of findings for the main comparison (Appendix 3) the required sample size was not achieved, so the quality of the evidence for each outcome was downgraded for imprecision (Guyatt 2011). As a result, all outcomes in the Summary of findings for the main comparison had moderate levels of quality of evidence.

Potential biases in the review process

Extensive electronic searches were conducted to search for relevant articles. As the databases we searched mostly included papers in the English language, it is possible that papers describing trials of statins for preventing VTE in other languages may not have been located. This review included published data only, and the unpublished data of the ongoing studies was not available. As our meta-analysis was based on published data, there may be selective reporting biases. This review is not a comprehensive review of the effects of statins on cardiovascular outcomes as we assessed these outcomes based on studies that assessed statins in the

primary prevention of VTE. So there might be selection bias for the cardiovascular outcomes.

Agreements and disagreements with other studies or reviews

Our results were consistent with other meta-analyses, which showed that statin use could reduce the incidence of all cases of VTE, provoked VTE, and DVT only; but that it did not reduce the incidence of unprovoked VTE and PE (Agarwal 2010; Pai 2011; Ray 2003b; Squizzato 2010). These results are consistent with case-control studies and cohort studies showing reduced risks of VTE (HERS; Huerta 2007; Lacut 2004; Lacut 2008; Ramcharan 2009; Ray 2001a; Smeeth 2009; Sørensen 2009). In a study by Doggen 2004, simvastatin was associated with a reduced risk of PE (OR 0.51, 95% CI 0.29 to 0.91) but pravastatin was not (OR 1.85, 95% CI 0.65 to 5.26). In a retrospective cohort study (Yang 2002), current statin use was not associated with a reduced risk of idiopathic VTE (RR 0.8, 95% CI 0.3 to 2.7). However, another meta-analysis of published and unpublished evidence from RCTs showed that allocation to statin therapy did not significantly reduce the risk of VTE events, with no evidence of heterogeneity between effects on DVT and effects on PE (Rahimi 2012). It is possible that including unpublished data on statin use in the primary prevention of VTE might change the effect size (Rahimi 2012). Our meta-analysis only included one RCT that compared a statin with placebo in the primary prevention of VTE, and the study showed that statin use could reduce the incidence of VTE. These conflicting results mean that we still need further well designed and reported VTE primary prevention studies to test the prevention effects of statins.

AUTHORS' CONCLUSIONS

Implications for practice

Available evidence showed that rosuvastatin was associated with a reduced incidence of VTE, but the evidence was limited to a single RCT and any firm conclusions and suggestions could not be drawn. Randomised controlled trials of statins (including rosuvastatin) are needed to evaluate their efficacy in the prevention of VTE.

Implications for research

Further double-blind randomised controlled trials (RCTs) of statins (including rosuvastatin) for preventing VTE are required to provide conclusive evidence. Trials evaluating these outcomes as primary endpoints should be large and of reasonable duration, to confirm the conclusions from the JUPITER trial. This systematic review only evaluated the efficacy of rosuvastatin in the prevention of VTE; other statins have not been tested in RCTs. Therefore, future trials should attempt to determine the efficacy of other statins for preventing VTE, whether this is a class effect seen with all statins, and whether the effect is dose-dependent. In addition, future prospective studies that carefully investigate the underlying mechanisms of the effects of statins in the prevention of VTE are strongly encouraged. Our review has a different conclusion from that by Rahimi 2012, suggesting that unpublished data from published RCTs may result in a different effect size. Therefore, we recommend that any RCTs investigating statins in the primary prevention of any disease should report VTE in their publications.

ACKNOWLEDGEMENTS

The review authors would like to thank the following people for commenting on the review: Marlene Stewart who helped revise the full review, Heather Maxwell who helped revise the protocol, Peng Zhang and WenQin Jia who gave some useful advice for this systematic review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

JUPITER trial

Methods	**Study type:** interventional
	Study design: RCT
	Allocation: randomised
	Control: placebo control
	Endpoint classification: safety and efficacy study
	Intervention model: parallel assignment
	Masking: double-blind

JUPITER trial *(Continued)*

	Primary purpose: prevention **Duration of study:** a median follow-up of 1.9 y (maximum: 5.0 y)
Participants	**Ages eligible for study:** 50 y and older **Genders eligible for study:** both **Accepts healthy volunteers:** no **Total number of subjects:** 17,802 **Location:** 1315 sites in 26 countries **Inclusion criteria:** men 50 y or older, women 60 y or older Low to normal levels of LDL cholesterol (< 130 mg/dL) Elevated levels of CRP > 2.0 mg/L **Exclusion criteria:** History of cardiovascular or cerebrovascular events Active liver disease DM Uncontrolled hypertension or hypothyroidism History of certain malignancies Chronic inflammatory conditions History of alcohol or drug abuse
Interventions	Rosuvastatin 20 mg daily Placebo 20 mg daily
Outcomes	**Primary outcome measures:** the rate of major cardiovascular events **Secondary outcome measures:** the safety of long-term treatment with rosuvastatin through comparisons of total mortality, non-cardiovascular mortality, and adverse events the incidence of DM, venous thromboembolic events, and bone fractures
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The method of randomisation was on the basis of a computer generated list
Allocation concealment (selection bias)	Low risk	Randomisation was performed with the use of an interactive voice-response system and was stratified according to centre
Blinding (performance bias and detection bias) All outcomes	Low risk	A closeout visit occurred after study termination, at which time participants were unblinded. All reported primary endpoints were adjudicated by an independent endpoint committee blinded to randomised treatment assignment.

JUPITER trial *(Continued)*

		Adverse events were monitored and reported in a blinded manner until the date of the closeout visit and discontinuation of therapy
Incomplete outcome data (attrition bias) All outcomes	Low risk	We compared study protocol and study publications, but we found no missing outcomes reported. There were no patients withdrawn and all patients were accounted for. There are no incomplete outcome data in this study
Selective reporting (reporting bias)	Low risk	We compared the protocol and the study publications and no outcomes were missed
Other bias	Low risk	The trial was financially supported by AstraZeneca. The authors of all publications reported that the sponsor collected the trial data and monitored the study sites but played no role in the conduct of the analyses or drafting of the manuscript. Therefore, funding should not have introduced potential biases in this trial

CRP: C-reactive protein
DM: diabetes mellitus
LDL: low density lipoprotein
y: years

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACCEPT-D	This study studied the effects of aspirin and simvastatin combination
AFCAPS/TexCAPS	The intervention in treatment group is diet and lovastatin, and the intervention in control group is diet
AIM-HIGH	All participants received simvastatin (or simvastatin plus ezetimibe) at a dose sufficient to maintain LDL- cholesterol. Participants were randomised to extended-release niacin or matching placebo
ASTRONOMER	This study did not report the VTE relevant outcomes
Caramelli 2002	This study did not report the VTE relevant outcome
CARDS	This study did not report the VTE relevant outcomes
ChiCTR-TNRC-08000263	Non-randomised control study
DECREASE III	This study did not report the VTE relevant outcomes
Doggen 2004	Case-control study
ELIMIT	A total of 102 patients were randomised to either mono-therapy with simvastatin (40 mg daily) or triple-therapy with simvastatin (40 mg daily), ER niacin (1500 mg daily), and ezetimibe (10 mg daily). This study did not report the VTE relevant outcomes
Ge 2011	This study did not report the VTE relevant outcomes
Haak 2001	This study did not report the VTE relevant outcomes
HERS	Cohort study

Study	Reason for exclusion
HPS2-THRIVE	This study compared ER niacin 2 g plus laropiprant 40 mg daily with placebo for occlusive arterial disease. This study did not report the VTE relevant outcomes
Huerta 2007	Case-control study
Jeong 2013	This study did not report the VTE relevant outcomes
Lacut 2004	Case-control study
Lacut 2008	Case-control study
LEADe	Mild to moderate Alzheimer's disease patients were receiving donepezil
Liu 2011	This study did not report the VTE relevant outcomes
MEGA	This study did not report the VTE relevant outcomes
METEOR	This study did not report the VTE relevant outcomes
NCT00437892	This study evaluated adult patients with a single episode of idiopathic VTE (either DVT or PE) who received at least 6 months of adequate treatment with oral anticoagulants, for whom treatment withdrawal is planned, and with LDL cholesterol levels of equal to or greater than 130 mg/dL, not evaluating the patients at risk of VTE
PROCEDURE	This is a study protocol and does not report on the relevant VTE outcomes
PROSPER	Case control study
Ramcharan 2009	Case-control study
RATIONAL	This study did not report the VTE relevant outcomes
Ray 2001a	Cohort study
Rosen 2013	This study compared switching to ezetimibe/simvastatin (EZ/S) 10/20 mg with doubling the run-in statin dose (to simvastatin 40 mg or atorvastatin 20 mg) or switching to rosuvastatin 10 mg in subjects with cardiovascular disease (CVD) and diabetes and did not report the VTE relevant outcomes
Shai 2014	Case-control study
Smeeth 2009	Cohort study
Stangier 2009	Authors focused on pharmacokinetics and pharmacodynamics, and did not mention all the outcomes we evaluated
Sørensen 2009	Case-control study
van der Loo 2011	This study did not report the VTE relevant outcomes
West 2010	This study compared simvastatin with simvastatin plus ezetimibe and did not report the VTE relevant outcomes
Yang 2002	Cohort study

DVT: deep vein thrombosis

ER: extended release
LDL: low density lipoprotein
PE: pulmonary embolism
VTE: venous thromboembolism

Characteristics of ongoing studies *[ordered by study ID]*

NCT00259662

Trial name or title	High-Dose Periop Statins for Prevention of DVT
Methods	Study type: interventional Study design: allocation randomised Intervention model: parallel assignment Masking: double-blind
Participants	Gynaecologic tumour scheduled for resection Exclusion criteria: prior reaction to statins renal insufficiency liver disease history of alcoholism prior history of DVT or hypercoagulability concurrent medications that significantly affect cytochrome P450 3A4 breast feeding or pregnancy
Interventions	Experimental arm: drug atorvastatin Control arm: unclear
Outcomes	**Primary outcome measures:** decrease in incidence of DVT **Secondary outcome measures:** decrease in inflammatory mediator release
Starting date	November 2005
Contact information	Yale - New Haven Hospital New Haven, Connecticut, United States, 06510 Contact: Ala S Haddadin, MD 203-785-2802 ala.haddadin@yale.edu Principal Investigator: Ala S Haddadin, MD
Notes	

NCT01021488

Trial name or title	Rosuvastatin for prevention of deep vein thrombosis in patients undergoing total knee replacement arthroplasty: STOP DVT - A prospective randomised controlled trial (NCT01021488)
Methods	Allocation: randomised Control: active control Endpoint classification: safety and efficacy study Intervention model: parallel assignment Masking: open label Primary purpose: prevention
Participants	Ages eligible for study: 19 y and older Genders eligible for study: both Accepts healthy volunteers: no **Criteria** **Inclusion criteria:** patients who are going to receive TKRA for any cause > 19 y old **Exclusion criteria:** patients with cancer; patients receiving anticoagulant agents for any cause current statin users expecting survival from other co-morbidity < 1 year bed-ridden patient AST, ALT > 3 times of UNL CK > UNL pregnancy patients who receive hormone replacement therapy
Interventions	Experimental arm: rosuvastatin + enoxaparin Rosuvastatin 20 mg/day for 7 days before and 7 days after index surgery, TKRA Enoxaparin 40 mg SQ/day 12 hr before TKRA and from 1 day to 7 day after TKRA should be administered at the same time with rosuvastatin Active comparator arm: enoxaparin only enoxaparin 40 mg SQ/day only starting 12hr before TKRA and from on day 1 to 7 after index surgery
Outcomes	**Primary outcome measures:** development of DVT diagnosed and confirmed by CT angiography at lower extremities (time frame: 7 days after index surgery) **Secondary outcome measures:** D-dimer, lipid panel (total cholesterol, TG, HDL, LDL), hsCRP, CK, transaminase, ALP (time frame: 7 days, 1 month, 2 months after index surgery)

NCT01021488 *(Continued)*

Starting date	October 2009
Contact information	Sang-Ho Jo, MD 82-31-380-3722 sophi5@medimail.co.kr
Notes	

NCT01063426

Trial name or title	Re-STOP DVT: Reload of High Dose Atorvastatin for Preventing Deep Vein Thrombosis in Statin Users
Methods	Study type: interventional Study design: allocation: randomised Endpoint classification: safety and efficacy study Intervention model: parallel assignment Masking: open label Primary purpose: prevention
Participants	Patients who are going to receive TKRA from any cause < 19 y old Exclusion criteria: patients with cancer patients receiving anticoagulant agents from any cause current statin users expecting survival from other co-morbidity < 1 y bed-ridden patient AST, ALT > 3 times of UNL CK > UNL pregnancy patients who receive hormone replacement therapy
Interventions	Experimental: atorvastatin + enoxaparin arm High dose atorvastatin arm before index surgery + conventional enoxaparin High dose atorvastatin 80 mg/day for 7 days after index surgery (TKRA). At the same time enoxaparin 40 mg SQ/day 12 hr before TKRA and from 1 day to 7 days after TKRA should be administered Active comparator: conventional enoxaparin Conventional enoxaparin before 12 hr and on 1 to 7 days after index surgery Drug: enoxaparin

NCT01063426 *(Continued)*

	Enoxaparin 40 mg SQ/day 12 hr before TKRA and on day 1 to day 7 after TKRA should be administered
Outcomes	**Primary outcome measures:** development of DVT diagnosed and confirmed by CT angiography at lower extremities **Secondary outcome measures:** D-dimer, lipid panel (total cholesterol, TG, HDL, LDL), hsCRP, CK, transaminase, ALP
Starting date	November 2009
Contact information	Hallym University Sacred Heart Hospital, Department of Cardiology and Orthopedic Surgery Anyang-si, Gyeonggi-do, Korea, Republic of, 431-070 Contact: Sang-Ho Jo, MD 82-31-380-3722 sophi5@medimail.co.kr
Notes	

NCT01524653

Trial name or title	Detecting the Impact of Statin Therapy On Lowering Risk of Venous Thrombo-Embolic Events (DISOLVE)
Methods	Study type: interventional Study design: allocation: randomised Endpoint classification: efficacy study Intervention model: crossover assignment Masking: double-blind (subject, caregiver, investigator, outcomes assessor) Primary purpose: prevention
Participants	Adult patients > 18 y old with locally-advanced or metastatic cancers who are about to start or are already receiving any systemic chemotherapy or targeted therapy Estimated overall survival of ≥ 6 months Anticipated duration of therapy ≥ 9 weeks (if 3 week cycle) or ≥12 weeks (if 2 or 4 week cycle). Systemic therapy is allowed to change if necessary, or to terminate, during this period **Exclusion criteria:** anti-thrombotic therapy including warfarin, dabigatran, LMWH or UFH. Patients taking aspirin may participate in this study anti-angiogenic therapy with thalidomide or lenalidomide. Patients receiving bevacizumab may participate in this study patients starting hormonal therapy exclusively, such as SERM or aromatase inhibitor therapy for breast cancer, or androgen-ablative therapy for prostate cancer statin use within 3 months prior to enrolment

NCT01524653 *(Continued)*

	adjuvant therapy in patients who have already received curative-intent local therapy (surgery or radiotherapy). Patients with glioblastoma starting adjuvant chemotherapy are an exception given the high likelihood of residual disease and risk of VTE in this population Asian descent as assessed by history. If either of the participant's parents is Asian (peoples of East, Southeast, and South Asia), a patient will be excluded due to slower metabolism of the drug and concerns regarding toxicity at the 20 mg dose level urinary creatinine clearance of less than 40 mL/min based on reported MDRD GFR, present in FAHC metabolic profile reports, during the 14 day screening period AST or ALT elevation of greater than 3X UNL during the 14 day screening period patients with a known history of statin intolerance that was accompanied by severe adverse reaction patients who are currently participating in another clinical trial involving an investigational medication if there is a known or suspected drug interaction with rosuvastatin or the statin class, or if the investigational agent is known or suspected to be associated with a significantly increased risk of thrombosis
Interventions	Experimental arm: rosuvastatin first, placebo last This arm will receive rosuvastatin during the first treatment period followed by placebo in the second treatment period after washout Drug: rosuvastatin 20 mg po od Drug: placebo 20 mg po od Control arm: placebo first, rosuvastatin last This arm will receive placebo during the first treatment period followed by rosuvastatin in the second treatment period after washout Drug: rosuvastatin 20 mg po od Drug: placebo 20 mg po od
Outcomes	**Primary outcome measures:** to determine if rosuvastatin therapy reduces the risk of VTE in patients with cancer receiving chemotherapy, as measured by a decrease in D-dimer level with treatment compared to placebo **Secondary outcome measures:** to investigate the impact of rosuvastatin therapy on other established bio-markers of VTE risk in cancer patients receiving chemotherapy as measured by the change in Factor VIII to investigate the impact of rosuvastatin therapy on other established bio-markers of VTE risk in cancer patients receiving chemotherapy as measured by the change in soluble P-selectin to investigate the impact of rosuvastatin therapy on other established bio-markers of VTE risk in cancer patients receiving chemotherapy as measured by the change in C-reactive protein to investigate the impact of rosuvastatin therapy on other established bio-markers of VTE risk in cancer patients receiving chemotherapy as measured by the change in Peak thrombin generation Adverse events (CTCAE v4) associated with rosuvastatin therapy liver toxicity and rhabdomyolysis venous thromboembolism (time frame: baseline, 3 to 4 weeks, 6 to 9 weeks, 9 to 13 weeks (ranges depending one treatment period lengths set for each patient at enrolment)

NCT01524653 *(Continued)*

	Clinical signs of VTE to investigate the impact of rosuvastatin therapy on other established bio-markers of VTE risk in cancer patients receiving chemotherapy as measured by the change in plasminogen activator inhibitor-1 activity to investigate the impact of rosuvastatin therapy on other established bio-markers of VTE risk in cancer patients receiving chemotherapy as measured by the change in plasminogen activator inhibitor-1 protein concentration to investigate the impact of rosuvastatin therapy on other established bio-markers of VTE risk in cancer patients receiving chemotherapy as measured by the change in tissue factor to investigate the impact of rosuvastatin therapy on other established bio-markers of VTE risk in cancer patients receiving chemotherapy as measured by the change in Factor XIa
Starting date	March 2012
Contact information	United States, Vermont Fletcher Allen Health Care Burlington, Vermont, United States, 05401
Notes	

ALP: alkaline phosphatase
ALT: alanine transaminase
AST: aspartate transaminase
CK: creatine kinase
CT: computed tomography
DVT: deep vein thrombosis
GFR: glomerular filtration rate
hr: hour
hsCRP: high-sensitivity C-reactive protein
HDL: high-density lipoprotein
LDL: low-density lipoprotein
LMWH: low molecular weight heparin
MDRD: modification of diet in renal disease
mg: milligrams
od: once daily
po: by mouth
SQ: subcutaneous
TG: triglycerides
TKRA: total knee replacement arthroplasty
UFH: unfractionated heparin
UNL: upper normal limit
VTE: venous thromboembolism
y: years

DATA AND ANALYSES

Comparison 1. Statin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cases of VTE	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Provoked VTE	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Deep vein thrombosis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Unprovoked VTE	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Pulmonary embolism	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 All cases of VTE - gender	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 men	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 women	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 All cases of VTE - age	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Aged 70 - 97 y	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Aged 50 - 69 y	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Cardiovascular events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9 Any MI	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10 Fatal MI	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11 Any stroke	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
12 Fatal stroke	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
13 Arterial revascularisation	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
14 Death	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
15 Death after VTE	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
16 Confirmed death resulting from cardiovascular causes	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
17 Any serious adverse event	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
18 Hepatic disorder	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
19 Myopathy	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
20 Rhabdomyolysis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21 Renal disorder	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
22 Bleeding	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
23 Muscular weakness, stiffness, or pain	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
24 Gastrointestinal disorder	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Statin versus placebo, Outcome 1 All cases of VTE.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	34/8901	60/8901		0%	0.57[0.37,0.86]

Favours rosuvastatin 0.5 0.7 1 1.5 2 Favours placebo

Analysis 1.2. Comparison 1 Statin versus placebo, Outcome 2 Provoked VTE.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	15/8901	29/8901		0.52[0.28,0.96]

Favours rosuvastatin 0.5 0.7 1 1.5 2 Favours placebo

Analysis 1.3. Comparison 1 Statin versus placebo, Outcome 3 Deep vein thrombosis.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	17/8901	38/8901		0.45[0.25,0.79]

Favours rosuvastatin 0.2 0.5 1 2 5 Favours placebo

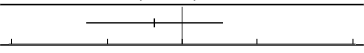
Analysis 1.4. Comparison 1 Statin versus placebo, Outcome 4 Unprovoked VTE.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	19/8901	31/8901		0.61[0.35,1.08]

Favours rosuvastatin 0.5 0.7 1 1.5 2 Favours placebo

Analysis 1.5. Comparison 1 Statin versus placebo, Outcome 5 Pulmonary embolism.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	17/8901	22/8901		0.77[0.41,1.46]

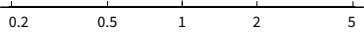


Analysis 1.6. Comparison 1 Statin versus placebo, Outcome 6 All cases of VTE - gender.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.6.1 men				
JUPITER trial	22/5475	44/5526		0.5[0.3,0.84]
1.6.2 women				
JUPITER trial	12/3426	16/3375		0.74[0.35,1.56]

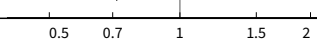
Analysis 1.7. Comparison 1 Statin versus placebo, Outcome 7 All cases of VTE - age.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.7.1 Aged 70 - 97 y				
JUPITER trial	15/2878	25/2817		0.59[0.31,1.11]
1.7.2 Aged 50 - 69 y				
JUPITER trial	19/6023	35/6084		0.55[0.31,0.96]



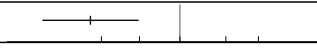
Analysis 1.8. Comparison 1 Statin versus placebo, Outcome 8 Cardiovascular events.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	134/7716	189/7832		0%	0.71[0.57,0.89]



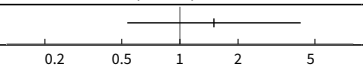
Analysis 1.9. Comparison 1 Statin versus placebo, Outcome 9 Any MI.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	31/8901	68/8901		0%	0.45[0.3,0.69]



Analysis 1.10. Comparison 1 Statin versus placebo, Outcome 10 Fatal MI.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	9/8901	6/8901		0%	1.5[0.53,4.22]



Analysis 1.11. Comparison 1 Statin versus placebo, Outcome 11 Any stroke.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	33/8901	64/8901		0%	0.51[0.34,0.78]

Analysis 1.12. Comparison 1 Statin versus placebo, Outcome 12 Fatal stroke.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	3/8901	10/8901		0%	0.3[0.08,1.09]

Analysis 1.13. Comparison 1 Statin versus placebo, Outcome 13 Arterial revascularisation.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	71/8901	131/8901		0%	0.54[0.4,0.72]

Analysis 1.14. Comparison 1 Statin versus placebo, Outcome 14 Death.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	198/8901	247/8901		0%	0.8[0.66,0.96]

Analysis 1.15. Comparison 1 Statin versus placebo, Outcome 15 Death after VTE.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	7/8901	14/8901		0.5[0.2,1.24]

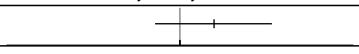
Analysis 1.16. Comparison 1 Statin versus placebo, Outcome 16 Confirmed death resulting from cardiovascular causes.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	19/8901	25/8901		0%	0.76[0.42,1.38]

Favours rosuvastatin — Favours placebo

Analysis 1.17. Comparison 1 Statin versus placebo, Outcome 17 Any serious adverse event.

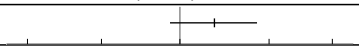
Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	622/8901	584/8901		0%	1.07[0.95,1.2]



Favours rosuvastatin — Favours placebo

Analysis 1.18. Comparison 1 Statin versus placebo, Outcome 18 Hepatic disorder.

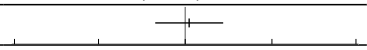
Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	216/8901	186/8901		0%	1.17[0.96,1.42]



Favours rosuvastatin — Favours placebo

Analysis 1.19. Comparison 1 Statin versus placebo, Outcome 19 Myopathy.

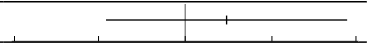
Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	10/8901	9/8901		1.11[0.45,2.74]



Favours rosuvastatin — Favours placebo

Analysis 1.20. Comparison 1 Statin versus placebo, Outcome 20 Rhabdomyolysis.

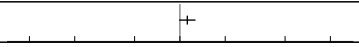
Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	1/8901	0/8901		3[0.12,73.66]



Favours rosuvastatin — Favours placebo

Analysis 1.21. Comparison 1 Statin versus placebo, Outcome 21 Renal disorder.

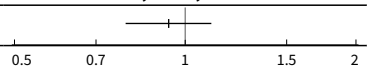
Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	535/8901	480/8901		0%	1.12[0.99,1.27]



Favours rosuvastatin — Favours placebo

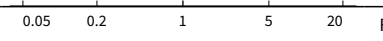
Analysis 1.22. Comparison 1 Statin versus placebo, Outcome 22 Bleeding.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	258/8901	275/8901		0.94[0.79,1.11]



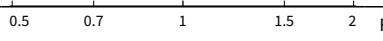
Analysis 1.23. Comparison 1 Statin versus placebo, Outcome 23 Muscular weakness, stiffness, or pain.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	1421/8901	1375/8901		0%	1.04[0.96,1.13]



Analysis 1.24. Comparison 1 Statin versus placebo, Outcome 24 Gastrointestinal disorder.

Study or subgroup	Rosuvastatin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
JUPITER trial	1753/8901	1711/8901		0%	1.03[0.96,1.11]



ADDITIONAL TABLES

Table 1. Published studies reporting the frequency of venous thromboembolism (VTE) in statin users and nonusers

Study	Type	No. of participants	Drug	Result
JUPITER trial	RCT (secondary outcome)	8901/8901	Rosuvastatin 20 mg daily versus placebo	HR 0.57 (95% CI 0.37 to 0.86)
Ramcharan 2009	Case-control	4538/5914	Any statin	OR 0.55 (95% CI 0.46 to 0.67)
Sørensen 2009	Case-control	5824/58240	Any statin	OR 0.74 (95% CI 0.63 to 0.85)
Smeeth 2009	Cohort study	129,288/600,241	Any statin	HR no statin versus statin 1.18 (95% CI 1.06 to 1.31)
Lacut 2004	Case-control	377/377	Any statin	OR 0.42 (95% CI 0.23 to 0.76)
Lacut 2008	Case-control	677/677	Any statin	OR 0.53 (95% CI 0.37 to 0.78)
HERS	Non-randomised comparison (part of HERS)	1712/1051	Any statin	HR 0.40 (95% CI 0.18 to 0.91)

Table 1. Published studies reporting the frequency of venous thromboembolism (VTE) in statin users and nonusers *(Continued)*

Yang 2002	Retrospective cohort study	22,993/61,100	Any statin	IRR current/recent statin use 0.8 (95% CI 0.3 to 2.7)
Ray 2001a	Retrospective cohort study	77,993/47,869	Any statin	HR 0.78 (95% CI 0.69 to 0.87)
Huerta 2007	Case-control	6,550/10,000	Any statin	OR 0.70 (95% CI 0.50 to 0.97)
Doggen 2004	Case-control	465/1962	Simvastatin, pravastatin	Simvastatin OR 0.51 (95% CI 0.29 to 0.91) Pravastatin OR 1.85 (95% CI 0.65 to 5.26)

CI: confidence interval
HERS: Heart and Estrogen/Progestin Replacement Study (HERS)
HR: hazard ratio
IRR: incidence rate ratio
OR: odds ratio

APPENDICES

Appendix 1. Risk factors for venous thromboembolism

(Buller 2005; Chapman 2009; Geerts 2008)

General	High risk clinical situations	Diseases associated with a prothrombotic state	Inherited thrombophilia
Older age Immobility, paresis Malignancy Obesity Previous VTE Family history of VTE Oral contraceptive pill, hormone replacement, tamoxifen Venous insufficiency or varicose veins	Surgery (especially hip and knee surgery or major surgery for malignancy) Pregnancy/puerperium Acute medical illness Congestive cardiac and respiratory failure Trauma Central venous catheter	Myeloproliferative disorders Antiphospholipid syndrome Paroxysmal nocturnal haemoglobinuria Nephrotic syndrome Hyperviscosity syndrome Inflammatory bowel disease	Factor V Leiden mutation Antithrombin, protein C and protein S deficiency Prothrombin gene mutation (Factor II G20210A mutation)

Appendix 2. CENTRAL search strategy

#1	MeSH descriptor: [Venous Thrombosis] explode all trees	2290
#2	MeSH descriptor: [Thromboembolism] explode all trees	1711
#3	MeSH descriptor: [Thrombosis] this term only	5223
#4	thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*	18177
#5	MeSH descriptor: [Pulmonary Embolism] this term only	914

(Continued)

#6	PE:ti,ab,kw	1828
#7	Pulmonary Embolism: ti, ab, kw	1778
#8	DVT* or VTE or ((vein* or ven*) near thromb*):ti,ab,kw	5925
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	20357
#10	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees	2766
#11	statin*:ti,ab,kw	3668
#12	hydroxymethylglutaryl*:ti,ab,kw	3484
#13	HMG CoA*:ti,ab,kw	708
#14	cholesterol near/4 inhibit*:ti,ab,kw	321
#15	MeSH descriptor: [Anticholesteremic Agents] this term only	4413
#16	(atorvastatin or cerivastatin or fluvastatin or lovastatin or pravastatin or simvastatin or *statin or lipitor or baycol or lescol or mevacor or altocor or pravachol or lipostat or zocor or rosuvastatin):ti,ab,kw	10066
#17	fluindostatin or dalvastatin or pitavastatin:ti,ab,kw	192
#18	mevinolin* or monacolin or lipex* or lipitor or lescol*:ti,ab,kw	150
#19	compactin or mevastatin or meglutol or crestor or zocor:ti,ab,kw	48
#20	3-hydroxy-3-methylglutar*:ti,ab,kw	336
#21	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20	11946
#22	#9 and #21 in Trials	422

Appendix 3. Trial sequential analysis results

For the outcomes in Summary of findings for the main comparison, we used TSA software to calculate the required sample size based on the event proportion in the control group; assumption of a plausible RR reduction of 20%; a risk of type I error of 5%; a risk of type II error of 20%; and the assumed diversity of the meta-analysis.

For all the seven outcomes in the Summary of findings for the main comparison, the sample sizes were lower than the required sample size.

However, for four outcomes, 'pulmonary embolism', 'any MI', 'any stroke' and 'any serious adverse event', the futility area was not reached before the required sample size. This suggests that the evidence was not sufficient and we need more RCTs before reaching a firm conclusion. For the remaining three outcomes, 'all cases of VTE', 'deep vein thrombosis', and 'death', the futility area was reached before the required sample size. This suggests that the cumulative evidence was conclusive for these three outcomes.

WHAT'S NEW

Date	Event	Description
11 September 2014	New citation required but conclusions have not changed	Searches rerun. No new studies included. Twenty-four additional studies excluded and three additional ongoing studies added. No change to conclusions.
11 September 2014	New search has been performed	Searches rerun, no new studies included. Twenty-four additional studies excluded and three additional ongoing studies added. Summary of findings table added. Review updated in keeping with current Cochrane policies.

CONTRIBUTIONS OF AUTHORS

Draft the protocol	Lun Li; JinHui Tian
Obtain copies of studies	TianTian Sun; Peizhen Zhang
Select which studies to include	Lun Li; JinHui Tian
Extract data from studies	Lun Li; JinHui Tian
Enter data into RevMan	Lun Li; Peizhen Zhang
Carry out the analysis	JinHui Tian; Lun Li
Interpret the analysis	KeHu Yang; JinHui Tian
Draft the final review	Lun Li; JinHui Tian
Update the review	Lun Li; JinHui Tian

DECLARATIONS OF INTEREST

None known

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Internal sources

- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the Primary outcomes section, we added the definition of provoked and unprovoked VTE because we wanted to distinguish between them, for healthy users and patients. Also, we changed 'all cause mortality' to 'the rate of death'.

We moved 'the rate of cardiovascular and cerebrovascular events' and 'the rate of death' to the Secondary outcomes section to highlight that the primary outcome of this review is 'the rate of VTE (DVT and PE)' and that the included studies were selected for the assessment of VTE and not cardiovascular and cerebrovascular events. We added 'serious adverse event (SAE)' to the Secondary outcomes section because we think this is an important outcome within the adverse events outcome.

In the updated review, we also analysed the data using the TSA software to judge whether the evidence is sufficient or not, and we have included a summary of findings table (Summary of findings for the main comparison).

INDEX TERMS

Medical Subject Headings (MeSH)

Fluorobenzenes [adverse effects] [*therapeutic use]; Hydroxymethylglutaryl-CoA Reductase Inhibitors [adverse effects] [*therapeutic use]; Myocardial Infarction [prevention & control]; Pyrimidines [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Rosuvastatin Calcium; Stroke [prevention & control]; Sulfonamides [adverse effects] [*therapeutic use]; Venous Thromboembolism [*prevention & control]; Venous Thrombosis [prevention & control]

MeSH check words

Female; Humans; Male; Middle Aged