Effect of Statins on Venous Thromboembolic Events: A Meta-analysis of Published and Unpublished Evidence from Randomised Controlled Trials

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Abstract

Background: It has been suggested that statins substantially reduce the risk of venous thromboembolic events. We sought to test this hypothesis by performing a meta-analysis of both published and unpublished results from randomised trials of statins.

Methods and Findings: We searched MEDLINE, EMBASE, and Cochrane CENTRAL up to March 2012 for randomised controlled trials comparing statin with no statin, or comparing high dose versus standard dose statin, with 100 or more randomised participants and at least 6 months' follow-up. Investigators were contacted for unpublished information about venous thromboembolic events during follow-up. Twenty-two trials of statin versus control (105,759 participants) and seven trials of an intensive versus a standard dose statin regimen (40,594 participants) were included. In trials of statin versus control, allocation to statin therapy did not significantly reduce the risk of venous thromboembolic events (465 [0.9%] statin versus 521 [1.0%] control, odds ratio [OR] = 0.89, 95% CI 0.78–1.01, $p = 0.08$) with no evidence of heterogeneity between effects on deep vein thrombosis (266 versus 311, OR 0.85, 95% CI 0.72–1.01) and effects on pulmonary embolism (205 versus 222, OR 0.92, 95% CI 0.76–1.12). Exclusion of the trial result that provided the motivation for our meta-analysis (JUPITER) had little impact on the findings for venous thromboembolic events (431 [0.9%] versus 461 [1.0%], OR = 0.93 [95% CI 0.82–1.07], $p = 0.32$ among the other 21 trials). There was no evidence that higher dose statin therapy reduced the risk of venous thromboembolic events compared with standard dose statin therapy (198 [1.0%] versus 202 [1.0%], OR = 0.98, 95% CI 0.80–1.20, $p = 0.87$). Risk of bias overall was small but a certain degree of effect underestimation due to random error cannot be ruled out.

Conclusions: The findings from this meta-analysis do not support the previous suggestion of a large protective effect of statins (or higher dose statins) on venous thromboembolic events. However, a more moderate reduction in risk up to about one-fifth cannot be ruled out.

Please see later in the article for the Editors' Summary.

Introduction

Venous thromboembolic disease (i.e., pulmonary embolism and deep vein thrombosis) is a common cause of premature death and morbidity [1–3], yet our knowledge about how to safely prevent it is limited. During recent years, statins have emerged as one of the most effective treatments to reduce the burden of arterial cardiovascular disease worldwide [4]. Because of their remarkably good safety profile and declining costs, there has been some interest in their potential use for prevention of other conditions, such as venous thromboembolic events [5–7]. Venous and arterial thrombosis often co-occur [8,9] and seem to share some common risk factors [10]. These epidemiological findings together with experimental evidence revealing novel mechanisms for the beneficial effect of statins unrelated to their low density lipoprotein (LDL) cholesterol lowering effect [11–13] have raised hopes that statins may also protect against venous thromboembolic events.

Until recently, clinical evidence for the effect of statins on venous thromboembolism was largely confined to non-randomised studies (with somewhat contradictory conclusions) [14,15]. In 2009, however, secondary analyses of the JUPITER trial, in which 17,802 apparently healthy men and women were randomly allocated to receive either rosuvastatin 20 mg daily or matching placebo, provided direct randomised evidence that statin therapy might reduce the risk of venous thromboembolic events [5]. In this trial, allocation to rosuvastatin was associated with a reduction in the risk of venous thromboembolic events of 43% (95% CI 14%–63%) during a median 1.9 y follow-up [5], but this was based on relatively few patients with a venous thromboembolic event (34 versus 60), and so may partly (or even wholly) reflect the play of chance [16]. This uncertainty was reflected by calls for confirmatory evidence from other studies [17,18]. An opportunity to obtain such evidence is provided by the routinely collected adverse event reports in existing statin trials. We therefore performed a meta-analysis of all larger scale trials of a statin versus control, and of a more intensive versus a less intensive statin regimen [19], which collected, but did not necessarily publish, information on the incidence of venous thromboembolic events during follow-up.

Methods

Ethics Statement

Ethics approval was not required for this work.

Search Strategy for Identification of Relevant Studies

PRISMA checklist is provided as Text S1. Study methods have been summarised in the study protocol (Text S2) and have been published previously [20]. In brief, we searched MEDLINE (January 1966 to March 2012), EMBASE (January 1985 to 2012 week 10), and the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, March 2012) for articles with a subject term "hydroxymethylglutaryl-coenzyme A reductase inhibitor" or any of the following terms: "hydroxymethylglutaryl-co A reductase inhibitor," "statin," "fluvastatin," "pravastatin," "lovastatin," "simvastatin," "atorvastatin," or "rosuvastatin." The search was limited to randomised controlled trials and human studies with no language restrictions.

Review Methods and Selection Criteria

Four reviewers, working in pairs, independently screened all titles and abstracts for randomised controlled trials with either a parallel or factorial design, with at least one comparison of a statin versus a control regimen or a more versus less intensive statin

regimen, and with a total of 100 or more randomised participants followed for at least 6 mo. Reviewing process was piloted for the first 100 abstracts by all four reviewers (KR, NB, Paul McGale, and William Majoni) to assess comparability and difficulties. Then, each abstract was independently reviewed by two researchers and disagreements resolved by retrieval of the full text article and discussion with a third person. There were no restrictions placed on participant characteristics or study outcomes. We also hand-searched the reference lists of these studies to ensure that other relevant articles, such as meta-analyses of statin trials or other types of articles related to statins and venous thromboembolic events, were not missed. After removing duplicate reports, full text articles of all remaining reports were examined.

Data Abstraction

For each trial, the following information was recorded: study or investigator's name; mean follow-up duration; year of publication of the primary findings; randomised treatments; mean LDL cholesterol at 1 y; summary information about the studied population (number of participants, mean age, number of men, and prevalence of myocardial infarction or heart failure at randomisation); and the primary outcome of the study. The number of patients with at least one reported episode of deep vein thrombosis or pulmonary embolism was recorded. In trials where information on such outcomes had not previously been published, we asked the investigators to abstract the relevant numbers from their routine records of adverse events. Non-responders were sent at least one reminder after about 3 wk and were also contacted by telephone.

Assessment of Risk of Bias

To identify potential sources of bias in the reported events we followed the Cochrane Collaboration's risk of bias framework [21] and considered for each trial the following risk domains: (i) selection bias (random sequence generation and allocation concealment); (ii) performance bias (blinding of participants and study investigators for the outcomes of interest); (iii) detection bias (blinding of outcome assessors); (iv) attrition bias (incomplete outcome data); (v) reporting bias (selective outcome reporting). Risk of bias for each domain was categorised as low, unclear, or high. This information was used to make judgements about the overall risk of bias for each trial. We followed the Cochrane Collaboration's recommendation to make judgements on the basis of whether the ranking of the level of bias across domains could have led to any material bias on the outcomes of interests and, where applicable, what the direction of the bias would likely be [21].

Statistical Analysis

Our primary hypothesis was to test whether statin treatment reduced the risk of venous thromboembolic events. The primary analyses were, therefore, restricted to trials of statin versus control (i.e., placebo or usual care). However, since the anti-inflammatory effect of statins (which could be a potential mechanism for any venous anti-thrombotic effects) have been suggested to be more pronounced in high-dose statin therapy [22] and since there is some non-randomised evidence to suggest a greater reduction in risk of venous thromboembolic events with higher doses of statins [19,23], we also performed secondary analyses on the basis of the trials that had compared a more intensive versus a standard statin regimen. Odds ratios (ORs) for each trial and summary estimates of ORs across trials were estimated using Peto's one-step method

(see Text S3) [24]. Estimates of heterogeneity between trials were presented together with I^2 statistics and their confidence intervals.

We performed three subgroup analyses: (i) to estimate effects separately for pulmonary embolism and deep vein thrombosis; (ii) to estimate effects separately in trials that specifically excluded patients with a known history of vascular disease compared with other trials; and (iii) to estimate effects separately according to the type of statin tested. The summary ORs for subgroups were compared using a standard chi-squared test. In a sensitivity analysis, we performed a meta-analysis of the individual trial results weighted by the absolute LDL cholesterol difference in each trial at 1 y (Text S3) [4].

Statistical analyses were done using R version 2.11.1 [25]. All statistical tests were two-sided and all analyses were done on an intention-to-treat basis.

Results

Out of 4,736 abstracts reviewed, 231 papers describing 112 trials were retrieved for further examination, of which 92 had both a follow-up duration of 6 mo or longer and had included 100 patients or more (Figure 1). Of these 92 trials, 47 trials comprising 54,643 participants and about 189,800 person-years' follow-up were excluded either because no venous thromboembolic events were recorded (i.e., zero events in both groups after interrogation of trial database) or because such information was not accessible to the trial investigators at the time. A further 16 trials comprising 7,846 participants and 18,200 person-years follow-up were excluded because there was no response to the data request. Our final database therefore included 29 trials comprising 146,353 participants and about 613,800 person-years follow-up. Of these, published information about venous thromboembolic events was available (at the time of our database search) from just two trials [5,26], but unpublished information was provided by authors for a further 27 trials. 22 trials compared the effect of statin with control (105,759 randomised participants and 422,000 person-years follow-up) [26–46], and seven trials compared a more intensive with a standard dose statin (40,594 randomised participants and 191,000 person-years follow-up) [47–53], with no overlap between the two trial groups [39]. The characteristics of the 29 included trials are shown in Table 1. Risk of bias for individual trials is summarised in Table 2. Risk of bias for venous thromboembolic events was deemed low for all included trials.

The primary analyses were restricted to the 22 trials that compared a statin with a control regimen. In these trials, an episode of venous thromboembolic event occurred in 986 patients. Overall, there was no clear evidence that statin therapy reduced the risk of venous thromboembolic events (465 [0.9%] statin versus 521 [1.0%] control, OR = 0.89 [95% CI 0.78–1.01]; $p = 0.08$) (Figure 2). There was no evidence of heterogeneity in estimated effect size between the trials (heterogeneity $\chi^2_{21} = 23$; $p = 0.34$) but a moderate degree of statistical inconsistency between the trials could not be ruled out ($I^2 = 0\%$, 95% CI 0%–43%). Since it was the result from the JUPITER trial that motivated us to perform this meta-analysis, it could be argued that that result should be considered only as "hypothesis generating," and that including it in the main analyses may have led to a summary point estimate, CI, and p-value that are appreciably biased [54,55]. Excluding this trial, however, had little effect on the overall result (431 [0.9%] versus 461 [1.0%], OR 0.93; 95% CI 0.82–1.07; $p = 0.32$) (Figure 2). Virtually identical results were seen when the individual trial results were weighted by the 1-y LDL cholesterol difference (in all 22 trials: OR 0.90 per mmol/l LDL cholesterol reduction, 95% CI 0.81–1.00; $p = 0.05$).

In the seven trials that compared a more intensive versus a standard statin regimen, there was no evidence that higher dose statin therapy reduced the risk of venous thromboembolic events compared with standard dose statin therapy (198 [1.0%] versus 202 [1.0%], respectively, OR 0.98; 95% CI 0.80–1.20; $p = 0.87$) and there was no evidence that the effect varied within these trials (heterogeneity $\chi^2_6 = 4.5$; $p = 0.61$) (Figure 3). However a moderate to large degree of statistical inconsistency between the trials could not be ruled out ($I^2 = 0\%$, 95% uncertainty level 0%–61%). The effect estimates weighted for 1-y LDL cholesterol differences were similar (weighted OR 0.99, 95% CI 0.66–1.51, per 1 mmol/l LDL cholesterol reduction).

To assess a possible differential effect of statins (or higher dose statins) on pulmonary embolism and deep vein thrombosis, we estimated the effects on each outcome separately. There was no good evidence that the effect of statin therapy differed by the type of outcome ($\chi^2_1 = 0.4$, $p = 0.54$ for heterogeneity for the trials of statin versus control, and $\chi^2_1 = 3.4$, $p = 0.06$ for heterogeneity for the trials of more intensive versus standard dose statin) (Figure 4). Nor was there evidence that either statin therapy or higher dose statin therapy significantly reduced the risk of either type of outcome in isolation (deep vein thrombosis: 266 versus 311, OR 0.85 [99% CI 0.69–1.06] for trials of statin versus control and 88 versus 106, OR 0.83 [99% CI 0.57–1.21] for trials of more versus less statin; pulmonary embolism: 205 versus 222, OR 0.92 [99% CI 0.72–1.19] for trials of statin versus control and 127 versus 107, OR 1.19 [99% CI 0.84–1.68] for trials of more versus less statin) (Figure 4).

In trials that exclusively studied patients with no previous history of cardiovascular disease [5,27,32,37,43–45], statin therapy was associated with a significant 38% reduction in the risk of venous thromboembolism (OR 0.62, 99% CI 0.41–0.94), which appeared to differ from the non-significant 4% reduction (OR 0.96, 99% CI 0.80–1.15) seen in other trials (p-value for heterogeneity between two groups of trials = 0.01) (Figure 5). However, there were no significant differences between the two groups of trials when the hypothesis-generating JUPITER trial was excluded from these analyses (p-value for heterogeneity between two groups of trials after exclusion of JUPITER = 0.20).

There was no good evidence that the effect of statin therapy on venous thromboembolism varied depending on type of statin studied ($\chi^2_5 = 10.7$, $p = 0.06$) (Figure S1), particularly when the results from the JUPITER trial were excluded ($\chi^2_5 = 5.8$, $p = 0.32$) (Figure S2).

Discussion

In this study, we gathered information from over 100,000 participants in 22 randomised trials of statin therapy versus control and 40,000 participants in seven randomised trials of intensive versus standard dose statin therapy, which together involve about 14 times as many venous thromboembolic events as previously reported in the JUPITER study [5]. Overall, the results from this meta-analysis do not support the suggestion that statins [5] (or higher doses of statins [19,23]) reduce the risk of venous thromboembolic events substantially, although a more moderate reduction in risk up to about one-fifth cannot be ruled out.

Our meta-analysis has several strengths compared to previous reports. Compared with previous publications that are either based on non-randomised comparisons or have been based on one single randomised trial with limited events, our findings are based on substantially more first events from randomised trials and, importantly, include previously unpublished as well as published data. Inclusion of unpublished data helps avoid the well-documented problems caused by the preferential publication of
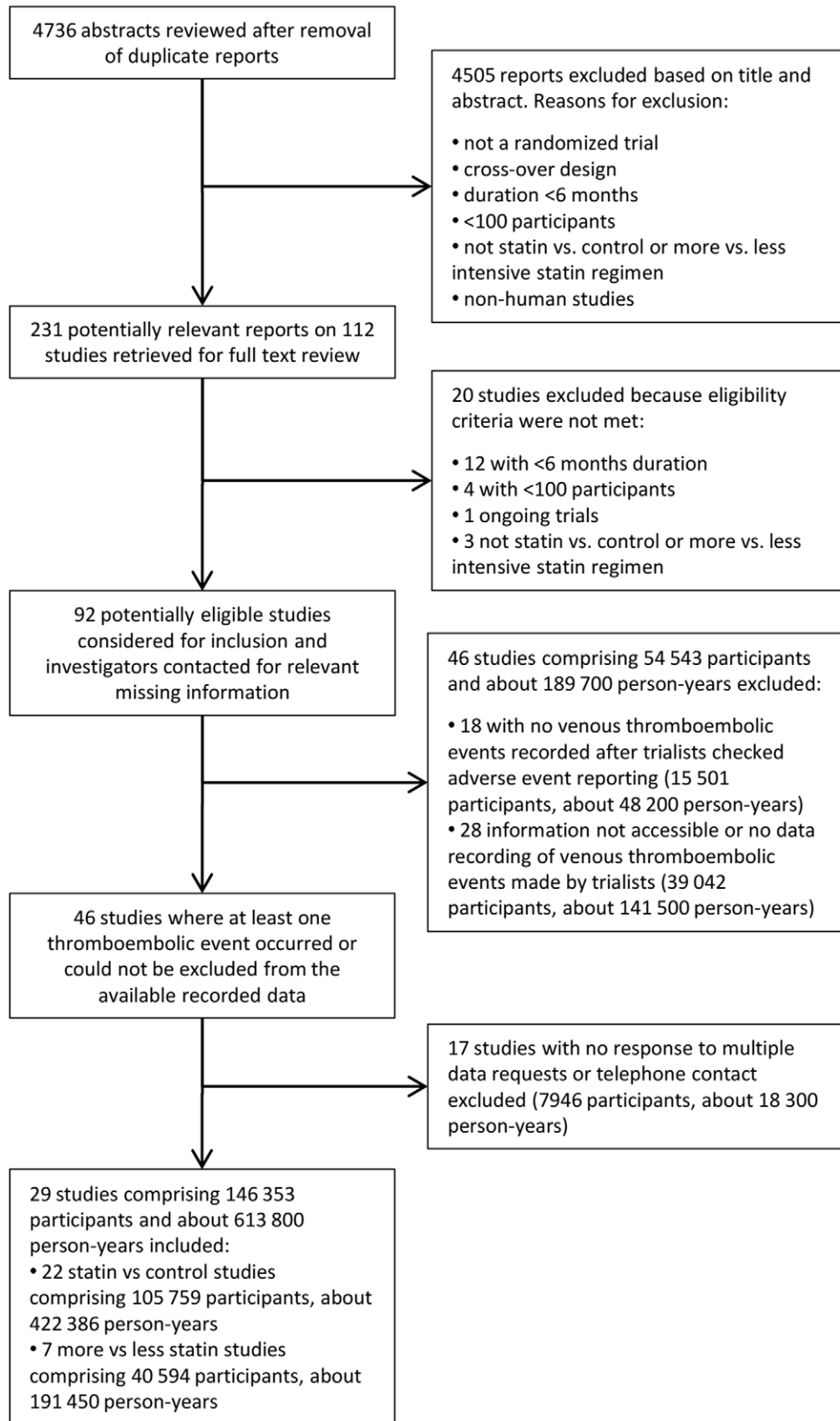
Figure 1. Flow-diagram of search retrieval process.
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Table 1. Summary of trials characteristics.

Study	Year of Publication of Main Results	Mean Follow-up (y)	Country/Region	Treatment Comparison		LDL-c Difference (mmol/l)[a]	Population Characteristics	Total *n* Participants	Mean Age (y)	Male (%)
				Intervention	Control Regimen		Main Inclusion Criteria			
Statin versus control regimen										
AFCAPS/TexCAPS [27]	1998	5.3	USA	L 20–40 mg	Placebo	0.94	Primary prevention	6,605	58	85
LIPID [28]	1998	5.6	Australia, New Zealand	P 40 mg	Placebo	1.03	History of MI or UA	9,014	62	83
HPS [29]	2002	5.0	UK	S 40 mg	Placebo	1.29	Vascular disease or diabetes	20,536	64	75
PROSPER [26]	2002	3.2	Scotland, Ireland, Netherlands	P 40 mg	Placebo	1.04	Elderly with vascular disease or high risk	5,699	75	47
ASCOT-LLA [30]	2003	3.2	Nordics and UK	A 10 mg	Placebo	1.07	Hypertension plus other risk factor	10,305	65	81
ALERT [31]	2003	5.1	Multinational	F 40 mg	Placebo	0.84	Renal transplant recipients	2,102	50	66
CARDS [32]	2004	3.9	UK, Ireland	A 10 mg	Placebo	1.14	Type 2 diabetes plus other risk factor	2,838	62	68
PREVEND IT [33]	2004	3.8	Netherlands	P 40 mg	Placebo	1.00	Microalbuminuric patients	864	51	65
ALLIANCE [34]	2004	4.3	USA	A 10–80 mg	Usual care	1.16	CHD	2,442	61	82
4D [35]	2005	3.9	Germany	A 20 mg	Placebo	0.89	Diabetic hemodialysis patients	1,255	66	54
SALTIRE [36]	2005	2.2	UK	A 80 mg	Placebo	1.74	Calcific aortic stenosis	155	68	70
MEGA [37]	2006	5.3	Japan	P 10–20 mg	No treatment	0.67	Primary prevention	7,832	58	30
ASPEN [38]	2006	4.3	Multinational	A 10 mg	Placebo	0.99	Type 2 diabetes	1,864	61	66
SPARCL [39]	2006	4.9	Multinational	A 80 mg	Placebo	1.43	Stroke or TIA, no CHD	4,731	63	60
CORONA [40]	2007	2.7	Multinational	R 10 mg	Placebo	1.61	Ischemic heart failure	5,011	73	76
Sola et al. [41]	2007	1.0	USA	A 20 mg	Placebo	0.81	Nonischemic heart failure	108	54	33
JUPITER [5]	2008	1.9	Multinational	R 20 mg	Placebo	1.09	Primary prevention	17,802	66	62
GISSI-HF [42]	2008	3.9	Italy	R 10 mg	Placebo	0.92	CHF	4,574	68	77
METEOR [43]	2009	2.0	Multinational	R 40 mg	Placebo	1.79	Primary prevention	981	60	57
LEADe [44]	2010	1.5	Multinational	A 80 mg	Placebo	0.30	Mild to moderate probable Alzheimer disease	640	74	48
ASTRONOMER [45]	2010	3.5	Canada	R 40 mg	Placebo	1.73	Mild to moderate aortic stenosis	269	58	61
LORD [46]	2010	2.5	Australia	A 10 mg	Placebo	0.80	Chronic kidney disease	132	62	65
More versus less intensive statin therapy										
ASAP [47]	2001	2.0	Netherlands	A 80 mg	S 40 mg	0.62	Familial hypercholesterolaemia	330	48	40
A-Z [48]	2004	2.0	Multinational	S 80 mg	S 20 mg	0.30	Acute coronary syndrome	4,497	61	75
REVERSAL [49]	2004	1.5	USA	A 80 mg	P 40 mg	0.97	>20% stenosis on routine coronary angiogram	657	56	72
PROVE IT [50]	2004	2.0	Multinational	A 80 mg	P 40 mg	0.65	Acute coronary syndrome	4,162	58	78

Table 1. Cont.

Study	Year of Publication of Main Results	Mean Follow-up (y)	Country/Region	Treatment Comparison		LDL-c Difference (mmol/l)[a]	Population Characteristics			
				Intervention	Control Regimen		Main Inclusion Criteria	Total *n* Participants	Mean Age (y)	Male (%)
TNT [51]	2005	4.9	Multinational	A 80 mg	A 10 mg	0.62	Clinically evident CHD	10,001	61	81
IDEAL [52]	2005	4.8	Nordics, Netherlands, Iceland	A 80 mg	S 20 mg	0.55	MI	8,888	62	81
SEARCH [53]	2010	6.7	UK	S 80 mg	S 20 mg	0.39	MI	12,064	62	81

[a]LDL-cholesterol differences are based on average differences between the two groups at 1 y (or the closest time to 1 y if 1 y data unavailable).
A, atorvastatin; CABG, coronary artery bypass graft surgery; CHD, coronary heart disease; CHF, chronic heart failure; L, lovastatin; MI, myocardial infarction; P, pravastatin; R, rosuvastatin; S, simvastatin; TIA, transient ischaemic attack.
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positive findings (i.e., publication bias) [16,56]. However, there is a perception among some that such unpublished data may be of inferior quality compared with data already in the public domain, despite the lack of evidence supporting such a view [21,57]. In our study, reports from all trials had previously been subject to external peer review and the risk of bias in these trials for the outcomes of interest was judged to be low in our assessments (Table 2). Most of the trials had a double-blind design (i.e., trial participants and investigators were unaware of the treatment allocation) and, perhaps more importantly, venous thromboembolic events had been collected routinely as part of the safety and efficacy monitoring done in each trial (at which point there were no specific hypotheses related to venous thromboembolic events) [26]. The use of routine unadjudicated events from these properly designed and conducted randomised trials is also unlikely to have resulted in any substantial biases because any under- or over-reporting of events (or, for that matter, lack of independent confirmation) would be expected to affect both treatment arms equally [20,58,59]. While systematic over-reporting of events unaffected by statin therapy would tend to bias treatment effects towards the null, the magnitude of the bias would again likely be small because OR estimates are surprisingly robust to such errors. For example, even if as much as one-quarter of the reported venous thromboembolic events in our study were "false" events that were unaffected by statin treatment (and hence equally distributed by treatment group), the estimate of the OR among the trials of statin versus control would have been expected to change from 0.89 (shown in Figure 2) to 0.86 as result of removal of the false events. Confirmation of diagnosis of symptomatic venous thromboembolism in routine clinical settings already depends on objective measures such as imaging and biochemistry. It therefore seems implausible that over-reporting of unrelated outcomes in these trials of the magnitude needed to result in substantial bias in OR estimates would have occurred. This is further supported by a recent study in which treatment effects based on adjudicated versus unadjudicated vascular events in ten trials involving over 9,000 events were compared, and found to be virtually identical (OR for reported versus adjudicated outcomes 1.00, 95% CI 0.97–1.02) [59]. Indeed, if anything, one might expect the reported outcomes in our study to be more consistent with "real-world" settings in effectiveness studies and, therefore, more relevant to policy and practice.

Another concern about inclusion of unpublished data in meta-analysis is incompleteness in trials gathered, which may itself become a source of bias [57]. In our study, we sought to obtain data from all larger trials, including repeated attempts at contacting study authors. However, we might still have missed relevant event information from at least 16 further trials where there was no response from investigators (in another 47 trials, either no events occurred or events were not available to the investigators themselves so would therefore not constitute a source of bias). However, these 16 trials would have contributed only about an additional 18,000 person-years of exposure (compared to about 600,000 person-years of exposure in the 29 included trials). In addition, if an important reduction in venous thromboembolism had been observed in any single trial for which data were not made available, it seems likely that the result may already have been published (as most of these trials were completed several years ago), and hence identified by our literature search. Thus, the relatively small amount of missing information is unlikely to have resulted in any material change to our conclusions. This is illustrated by a recent similar study that assessed the effect of statin on atrial fibrillation [20]. Additional data on this outcome from a larger statin trial became available only after the meta-analysis that combined both published and unpublished data were
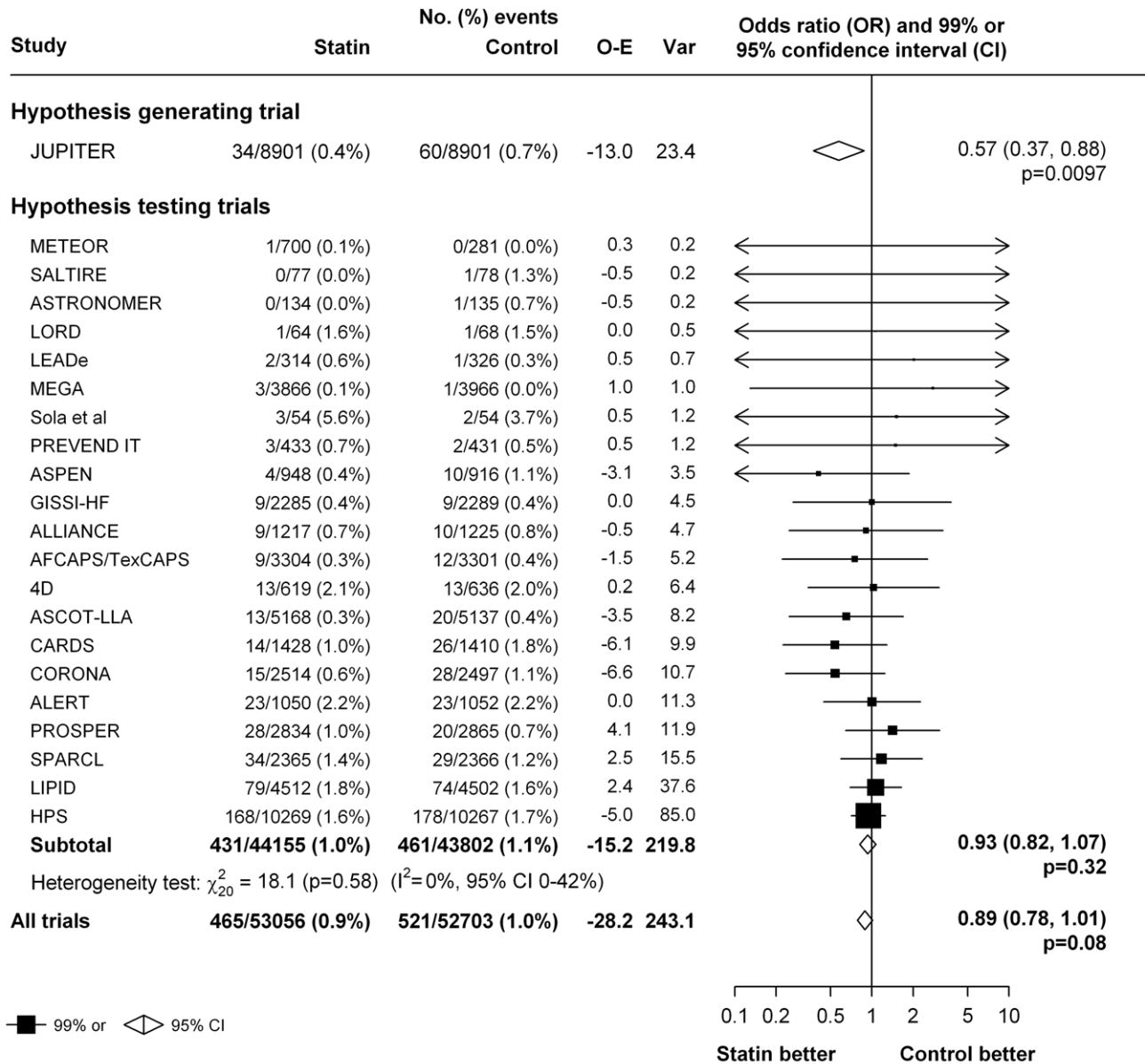
Table 2. Outcome determination and risk of bias for venous thromboembolic events.

Study	VTE Outcome Determination		Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk of Bias
	Adjudicated	Reported as Adverse Event Only						
Statin versus control regimen								
AFCAPS/TexCAPS [27]	No	Yes	Low	Low	Low	Low	Low	Low
LIPID [28]	No	Yes	Low	Low	Low	Low	Low	Low
HPS [29]	No	Yes	Low	Low	Low	Low	Low	Low
PROSPER [26]	Yes	Yes	Low	Low	Low	Low	Low	Low
ASCOT-LLA [30]	No	Yes	Low	Low	Low	Low	Low	Low
ALERT [31]	No	Yes	Low	Low	Low	Low	Low	Low
CARDS [32]	No	Yes	Low	Low	Low	Low	Low	Low
PREVEND IT [33]	No	Yes	Low	Low	Low	Low	Low	Low
ALLIANCE [34]	No	Yes	Unclear	Low	Low	Low	Low	Low
4D [35]	No	Yes	Low	Low	Low	Low	Low	Low
SALTIRE [36]	No	Yes	Unclear	Low	Low	Low	Low	Low
MEGA [37]	No	Yes	Low	Low	Low	Low	Low	Low
ASPEN [38]	No	Yes	Low	Low	Low	Low	Low	Low
SPARCL [39]	No	Yes	Low	Low	Low	Low	Low	Low
CORONA [40]	No	Yes	Low	Low	Low	Low	Low	Low
Sola et al. [41]	No	Yes	Unclear	Low	Low	Low	Low	Low
JUPITER [5]	Yes	No	Low	Low	Low	Low	Low	Low
GISSI-HF [42]	No	Yes	Low	Low	Low	Low	Low	Low
METEOR [43]	No	Yes	Low	Low	Low	Low	Low	Low
LEADe [44]	No	Yes	Low	Low	Low	Low	Low	Low
ASTRONOMER [45]	No	Yes	Low	Low	Low	Low	Low	Low
LORD [46]	No	Yes	Low	Low	Low	Low	Low	Low
More versus less intensive statin therapy								
ASAP [47]	No	Yes	Unclear	Low	Low	Low	Low	Low
A-Z [48]	No	Yes	Low	Low	Low	Low	Low	Low
REVERSAL [49]	No	Yes	Low	Low	Low	Low	Low	Low
PROVE IT [50]	No	Yes	Low	Low	Low	Low	Low	Low
TNT [51]	No	Yes	Unclear	Low	Low	Low	Low	Low
IDEAL [52]	No	Yes	Low	Low	Low	Low	Low	Low
SEARCH [53]	Yes (for PE)	No	Low	Low	Low	Low	Low	Low

Selection bias is based on random sequence generation and allocation concealment; performance bias includes blinding of participants and study investigators for the outcomes of interest; detection bias includes blinding of outcome assessors; attrition bias indicates systematic loss of participants in one arm, which could lead to missing outcome data for that trial arm over the other trial arm; and reporting bias includes the possibility of selective outcome reporting. Selection bias is a feature of the trial design. Performance and detection bias are overall low given that most data were collected without any prior knowledge of the investigators of the tested hypothesis in this study at the time of event collection. All analysis in this report are based on intention-to-treat and we further mitigated the possible effect of any attrition bias and reporting bias at individual trial level by collection of additional unpublished data.

PE, pulmonary embolism; VTE, venous thromboembolic event.

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Study	Statin	Control	O-E	Var	Odds ratio (OR) and 99% or 95% confidence interval (CI)	
		No. (%) events				
Hypothesis generating trial						
JUPITER	34/8901 (0.4%)	60/8901 (0.7%)	-13.0	23.4		0.57 (0.37, 0.88) p=0.0097
Hypothesis testing trials						
METEOR	1/700 (0.1%)	0/281 (0.0%)	0.3	0.2		
SALTIRE	0/77 (0.0%)	1/78 (1.3%)	-0.5	0.2		
ASTRONOMER	0/134 (0.0%)	1/135 (0.7%)	-0.5	0.2		
LORD	1/64 (1.6%)	1/68 (1.5%)	0.0	0.5		
LEADe	2/314 (0.6%)	1/326 (0.3%)	0.5	0.7		
MEGA	3/3866 (0.1%)	1/3966 (0.0%)	1.0	1.0		
Sola et al	3/54 (5.6%)	2/54 (3.7%)	0.5	1.2		
PREVEND IT	3/433 (0.7%)	2/431 (0.5%)	0.5	1.2		
ASPEN	4/948 (0.4%)	10/916 (1.1%)	-3.1	3.5		
GISSI-HF	9/2285 (0.4%)	9/2289 (0.4%)	0.0	4.5		
ALLIANCE	9/1217 (0.7%)	10/1225 (0.8%)	-0.5	4.7		
AFCAPS/TexCAPS	9/3304 (0.3%)	12/3301 (0.4%)	-1.5	5.2		
4D	13/619 (2.1%)	13/636 (2.0%)	0.2	6.4		
ASCOT-LLA	13/5168 (0.3%)	20/5137 (0.4%)	-3.5	8.2		
CARDS	14/1428 (1.0%)	26/1410 (1.8%)	-6.1	9.9		
CORONA	15/2514 (0.6%)	28/2497 (1.1%)	-6.6	10.7		
ALERT	23/1050 (2.2%)	23/1052 (2.2%)	0.0	11.3		
PROSPER	28/2834 (1.0%)	20/2865 (0.7%)	4.1	11.9		
SPARCL	34/2365 (1.4%)	29/2366 (1.2%)	2.5	15.5		
LIPID	79/4512 (1.8%)	74/4502 (1.6%)	2.4	37.6		
HPS	168/10269 (1.6%)	178/10267 (1.7%)	-5.0	85.0		
Subtotal	**431/44155 (1.0%)**	**461/43802 (1.1%)**	**-15.2**	**219.8**		0.93 (0.82, 1.07) p=0.32
Heterogeneity test: χ^2_{20} = 18.1 (p=0.58) (I^2=0%, 95% CI 0-42%)						
All trials	**465/53056 (0.9%)**	**521/52703 (1.0%)**	**-28.2**	**243.1**		0.89 (0.78, 1.01) p=0.08

0.1 0.2 0.5 1 2 5 10

Statin better   **Control better**

■— 99% or   ◇ 95% CI

Test for difference between JUPITER and combined result from other trials: χ^2_1 = 5.0 (p = 0.03)

Figure 2. Effect of statin therapy on venous thromboembolism.
doi:10.1371/journal.pmed.1001310.g002

published and this new information was entirely consistent with the pooled evidence [60].

Nonetheless, it should be recognised that the total number of first events in our meta-analysis (about 1,000 first reports of venous thromboembolism) is still relatively modest, as reflected by the confidence intervals that are consistent with anything from no effect to a real reduction in risk of about one-fifth. This makes the results of any subgroup analyses particularly unreliable, and so they need to be interpreted with due caution [54]. Consequently, this study cannot reliably investigate the potential differential effect of statins (or higher dose statins) in certain subgroups of patients based on important baseline characteristics such as prior history of venous thromboembolic events and use of anti-platelet or anti-coagulant therapy, or by the underlying cause of such events (e.g., provoked by cancer or other events versus unprovoked events).

Similarly, the suggested heterogeneity in effects on venous thromboembolism by prior vascular disease (Figure 5) is far from definitive. While it may be considered biologically plausible for there to be a proportionally smaller effect among people with pre-existing vascular disease or other chronic conditions (if the risk of venous thromboembolic events were less amenable to statin therapy as the proportion of events that are provoked by causes
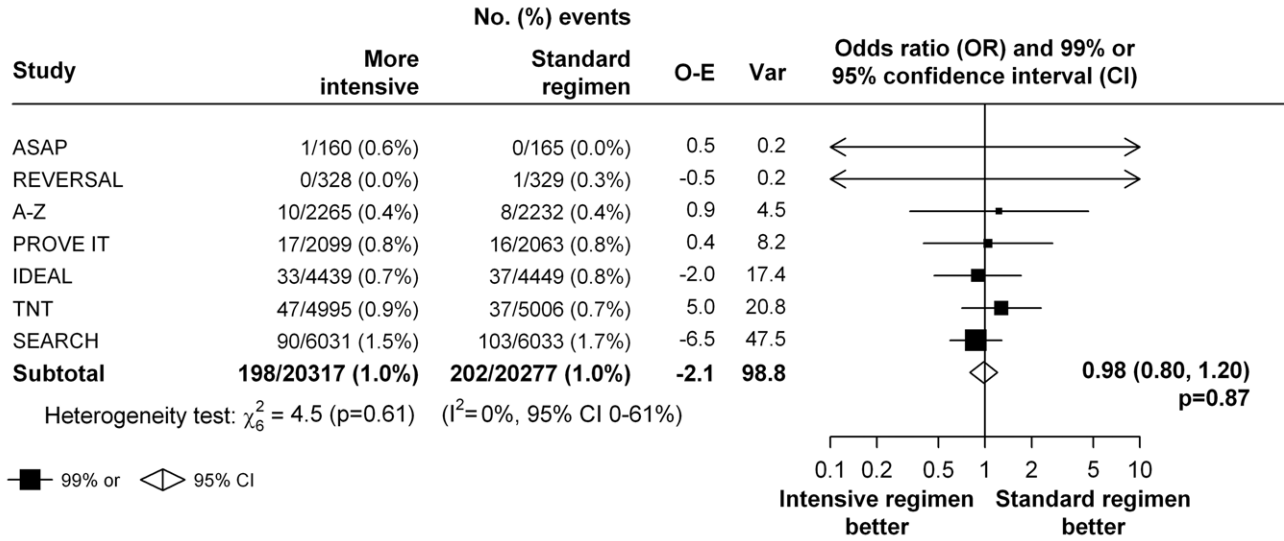
Figure 3. Effect of more intensive versus standard statin therapy on venous thromboembolism.
doi:10.1371/journal.pmed.1001310.g003

such cancer or immobility increases), the difference seen between trials that included healthier populations and those that did not was not statistically significant when the hypothesis-generating JUPITER trial was excluded (Figure 5). The same observation was made with regards to type of statins used (Figures S1 and S2). Thus, to demonstrate such differences (if one were to exist) would require further evidence from randomised trials.

Might the results be biased in favour of statin therapy owing to the interdependency of venous and arterial thrombosis? Statins reduce the risk of arterial vascular events (including hospitalisations) substantially [4], and more intensive regimens produce further definite reductions in risk [61]. One might therefore expect the number of venous thromboembolic events (some of which are related to arterial cardiovascular events [8,9]) to have been greater
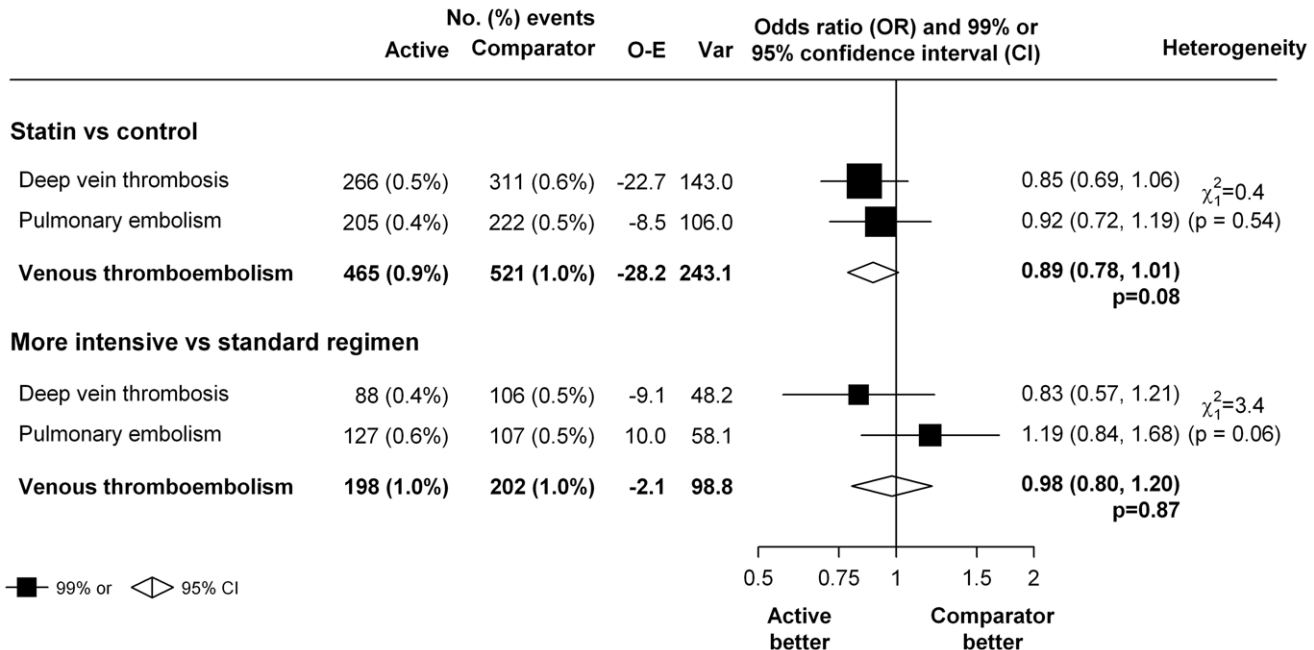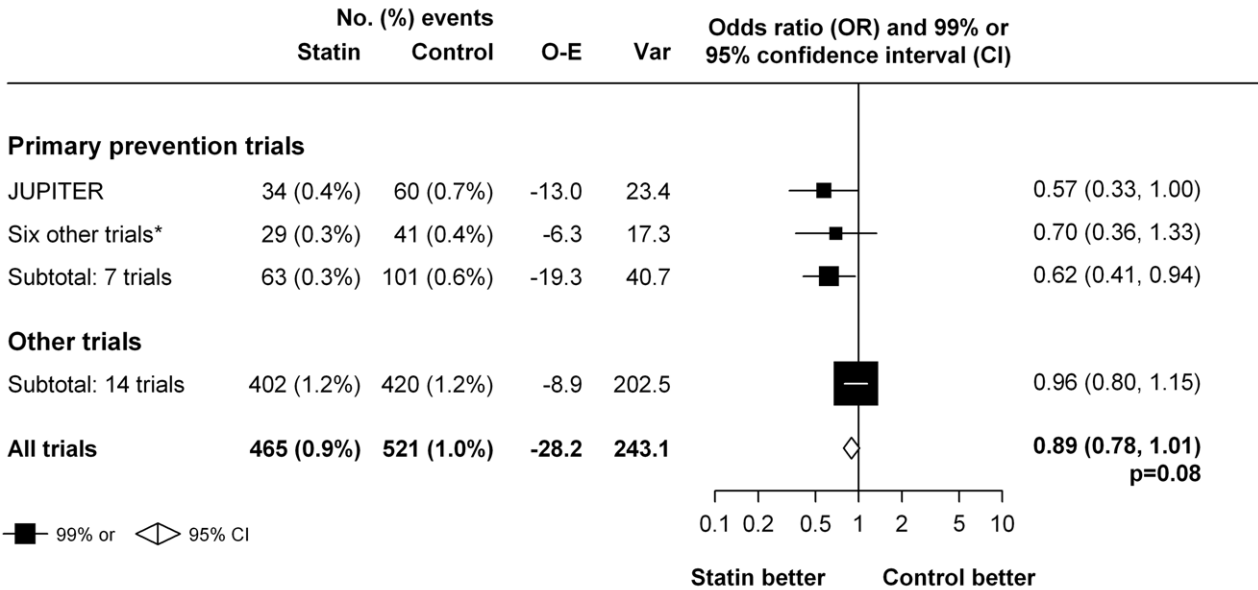

Figure 4. Effect of statin therapy on separate components of venous thromboembolism.
doi:10.1371/journal.pmed.1001310.g004

Figure 5. Effect of statin therapy on venous thromboembolism in primary cardiovascular prevention trials compared with other trials.
doi:10.1371/journal.pmed.1001310.g005

among patients allocated placebo/less intensive statin regimens. While this may be plausible, it seems likely that the incidence of venous thromboembolic events following a cardiovascular event would be low (for example only six out of the 94 events in JUPITER occurred following a cardiovascular event) and so unlikely to have introduced any substantial bias in favour of statins.

In conclusion, this study provides a more detailed assessment of the potential effects of statins (or higher dose statins) on venous thromboembolic events than has previously been possible. We were unable to confirm the large proportional reduction in risk suggested by some previous studies. However, a more modest but perhaps clinically worthwhile reduction in venous thrombo-embolic events in some or all types of patient cannot be ruled out.

Supporting Information

Text S1 PRISMA checklist.
(DOC)

Text S2 Study protocol.
(DOC)

Text S3 Statistical methods.
(DOCX)

Figure S1 Effect of statin therapy on venous thromboembolism, by type of statin.
(TIF)

Figure S2 Effect of statin therapy on venous thromboembolism, by type of statin, excluding JUPITER trial.
(TIF)

Author Contributions

Conceived and designed the experiments: KR NB PK. Analyzed the data: KR JE. Contributed reagents/materials/analysis tools: KR NB PK JE SB

VK MR JW JM. Wrote the first draft of the manuscript: KR. Contributed to the writing of the manuscript: KR NB PK JE SB VK JW JM. ICMJE criteria for authorship read and met: KR NB PK JE SB VK MR JW JM.

Agree with manuscript results and conclusions: KR NB PK JE SB VK MR JW JM.

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Editors' Summary

Background. Blood normally flows smoothly throughout the human body, supplying its organs and tissues with oxygen and nutrients. But, when an injury occurs, proteins called clotting factors make the blood gel (coagulate) at the injury site. The resultant blood clot (thrombus) plugs the wound and prevents blood loss. Occasionally, however, a thrombus forms inside an uninjured blood vessel and partly or completely blocks the blood flow. A clot inside one of the veins (vessels that take blood towards the heart) deep within the body is called a deep vein thrombosis (DVT). Symptoms of DVT (which usually occurs in the leg) include pain, swelling, and redness in the affected limb. DVT is treated with heparin and warfarin, two anticoagulant drugs that stop the blood clot growing. If left untreated, part of the clot (an embolus) can break off and travel to the lungs, where it can cause a pulmonary embolism (PE), a life-threatening condition characterized by chest pain, breathlessness, coughing, and dizziness. Little is known about how to prevent DVTs and PEs but risk factors for these venous thromboembolic events include having an inherited blood clotting disorder, oral contraceptive use, having surgery, and prolonged inactivity (on long-haul plane flights, for example).

Why Was This Study Done? In 2009, a secondary (add-on) analysis of data from a randomized controlled trial (RCT, a study that randomly assigns individuals to receive different treatments and compares the outcomes associated with each treatment) called the JUPITER trial reported that rosuvastatin—a cholesterol-lowering drug (statin)—halved the risk of venous thromboembolic events among apparently healthy adults. The JUPITER trial was initiated to test whether statins reduce the risk of strokes, heart attacks, and other cardiovascular diseases (conditions that involve the heart and the blood vessels) among adults with raised levels of a predictor for these diseases called C-reactive protein; statins reduce the levels of this protein as well as those of cholesterol. Because fewer than 100 of the participants in the JUPITER trial developed a DVT or PE, the reduction in the risk of a venous thromboembolic event among the participants who took rosuvastatin could have happened by chance. In this systematic review and meta-analysis of 29 RCTs of statins that collected information on many more venous thromboembolic events, the researchers test the hypothesis that statins substantially reduce the risk of such events. A systematic review uses predefined criteria to identify all the research on a given topic; a meta-analysis is a statistical approach that combines the results of several studies.

What Did the Researchers Do and Find? The researchers identified 22 RCTs (105,759 participants) that compared the effects of statins with control (dummy) tablets and seven (40,594 participants) that compared an intensive statin regimen with a standard regimen. They then obtained largely unpublished information about the venous thromboembolic events that occurred during these trials (about 1,000 DVTs and PEs) from the original investigators. In the trials of statin versus control, allocation to statin therapy did not significantly reduce the risk of venous thromboembolic events. Thus, although events occurred in 465 participants who were given statins (0.9% of the participants) and in 521 participants who were given control tablets (1% of the participants), this difference in outcomes was not statistically significant—it could have happened by chance. Exclusion of the JUPITER trial results from the meta-analysis did not alter this finding. The researchers also found no evidence that intensive statin therapy reduced the risk of venous thromboembolic events compared to standard therapy.

What Do These Findings Mean? The findings of this meta-analysis do not support the suggestion that statins, either at the standard dose or at higher doses, reduce the risk of venous thromboembolic events substantially among healthy adults. It is possible that the effect of statins has been underestimated in this meta-analysis because of missing data or because of some other source of bias. Furthermore, because the total number of events in this meta-analysis is still relatively modest, these findings do not rule out the possibility that statins may reduce the risk of venous thromboembolic events by up to about one-fifth in some or all individuals. Additional large RCTs are now needed to investigate whether statin treatment does in fact reduce the risk of venous thromboembolic events in adults and, if it does, whether all statins have a similar effect and whether statin treatment is beneficial in everyone or only in specific subgroups of people.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1001310.

- This study is further discussed in a *PLOS Medicine* Perspective by Frits Rosendaal
- The US National Heart Lung and Blood Institute provides information on deep vein thrombosis (including an animation about how DVT causes pulmonary embolisms), and information on pulmonary embolism
- The UK National Health Service Choices website has information on deep vein thrombosis, including personal stories, on pulmonary embolism, and on statins; a "Behind the Headlines" article describes the JUPITER trial and its implications
- The non-profit organization US National Blood Clot Alliance provides detailed information about deep vein thrombosis and pulmonary embolism for patients and professionals and includes a selection of personal stories about these conditions
- MedlinePlus has links to further information about deep vein thrombosis, pulmonary embolism, and statins (in English and Spanish)