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Chapter 3

Effect of statins on venous thromboembolic events: meta-analysis of published and unpublished evidence from randomised controlled trials

Kazem Rahimi, Neeraj Bhala, Pieter W Kamphuisen, Jonathan Emberson, Sara Biere-Rafi, Vera Krane, Michele Robertson, John Wikstrand, John McMurray

Submitted for publication

ABSTRACT

Background Limited evidence suggests that statins may reduce the risk of venous thromboembolic events. We sought to test whether this could be confirmed in a comprehensive assessment of published and unpublished results from larger scale statin trials.

Methods We searched MEDLINE, EMBASE and the Cochrane's CENTRAL up to October 2010 for randomised controlled trials comparing statin with no statin, or comparing high dose versus standard dose statin, with 100 participants or more and at least 6 months follow-up. Investigators were contacted for unpublished information about venous thromboembolic events.

Results Twenty one trials of statin versus control (105 636 participants) and seven trials of an intensive versus a standard dose statin regimen (40 594 participants) were included. In trials of statin versus control, statin therapy did not significantly reduce the risk of venous thromboembolic events (464 vs 520 statin vs control, odds ratio [OR]=0.89, 95% confidence interval [CI] 0.78 to 1.01, p=0.07) and treatment effects did not differ significantly between deep vein thrombosis or pulmonary embolism (p for heterogeneity=0.56). Exclusion of the trial that formed the hypothesis (JUPITER) had no material impact on the findings (430 vs 460, OR=0.93, 95% CI 0.82 to 1.06, p=0.30). There was no evidence that higher dose statin therapy reduced the risk of venous thromboembolic events (167 vs 152, OR=1.10, 95% CI 0.88 to 1.37, p=0.41).

Conclusion Findings from this study do not support the previous suggestion of a substantial protective effect of statins or higher dose statins on venous thromboembolic events.

INTRODUCTION

Venous thromboembolic disease (ie, pulmonary embolism and deep vein thrombosis) is a common cause of premature death and morbidity.[1] Yet, our knowledge about how to safely prevent it is limited. Since venous thrombosis appears to share some common pathological pathways with arterial disease,[2,3] there has been some interest to assess whether treatments of known efficacy for one disease process may also have similar effects in the other.

Statins reduce the risk of arterial cardiovascular disease in a wide range of people.[4] However, their effect on venous thromboembolic events is less certain. Until recently, clinical evidence for the effect of statins and venous thromboembolism was largely confined to non-randomised studies with somewhat contradictory findings.[5,6] The randomised JUPITER trial, which was designed to assess the effect of rosuvastatin compared to placebo on arterial cardiovascular events, reported in a substudy that treatment with rosuvastatin almost halves the risk of venous thromboembolic events.[7] However, this finding was based on relatively small numbers of events (34 vs 60), which on its own may not be sufficiently robust to change clinical practice recommendations. Conduct of new large-scale randomised statin trials with venous thromboembolic events as the primary outcome, however, may pose numerous practical and ethical challenges to test this hypothesis independently. In the absence of such trials, the wealth of available information from many completed large-scale randomised trials that have collected but not necessarily published information on venous thromboembolic events offers a unique opportunity to address this clinically important question.

To explore this question further, we set out to perform a meta-analysis of all larger scale trials of a statin versus control, and of a more intensive versus a less intensive statin regimen, which have collected, but not necessarily published, data on venous thromboembolic events.

METHODS

Search strategy for identification of relevant studies

Study methods have been published previously.[8] In brief, we searched MEDLINE (January 1966 to October 2010), EMBASE (January 1985 to 2010 week 40) and the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 4, October 2010) 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 with no language restrictions.

Review methods and selection criteria

Two reviewers 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 months. 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; 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 three weeks and were contacted by telephone.

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 (ie, placebo or usual care). However, since the anti-inflammatory effect of statins, as one of the potential mechanisms for their potential anti-thrombotic effects, have been suggested to be more pronounced in high-dose statin therapy,[9] and since there is some non-randomised evidence to suggest a greater reduction in risk of venous thromboembolic events with higher doses of statins,[10] we also performed secondary analyses based on the trials that had compared a more intensive versus a standard statin regimen.

For every trial, the "observed minus expected" statistic (o – e) and its variance (v) were calculated from the number of patients that developed venous thromboembolic events and the total number of patients in each treatment group, using standard formulae for 2x2 contingency tables. These (o – e) values, one from every trial, were summed to produce a grand total (G), with variance (V) equal to the sum of their separate variances. The value exp(G/V) is Peto's "one-step" estimate of the odds ratio and its continuity-corrected 95% confidence interval is given by $\exp(G/V \pm [0.5/V + 1.96/\sqrt{V}])$.[11] Odds ratios are given with 95% confidence intervals for the overall results and with 99% confidence intervals (replacing 1.96 in the formula above by 2.576) for individual trial results and subgroup results. The heterogeneity between the different trials was assessed by calculating

$S - G^2/V$, where S is the sum of $(o - e)^2/v$ for each trial, and testing this statistic against a chi-squared distribution with degrees of freedom equal to one less than the number of trials. In forest plots, trials are shown in order of the amount of statistical information they contribute to the overall result. We performed two subgroup analyses (i) to look at the differential effect of statins on pulmonary embolism and deep vein thrombosis and (ii) to assess whether treatment effects differed by the type of statin prescribed. The summary odds ratios for subgroups were compared using a standard chi-squared test.

Statistical analyses were done using R version 2.2.1.[12] All statistical tests were two-sided and all analyses were done on an intention-to-treat basis.

RESULTS

Out of 4033 abstracts reviewed, 218 papers describing 101 trials were retrieved for further examination, 83 of which met the inclusion criteria (Figure 1). Out of these 83 trials, published information about venous thromboembolic events was available only from one trial (ie, the hypothesis generating trial) at the time of our database search.[7] We contacted the investigators of the remaining 82 studies and were able to collect information from 27 trials where at least one thromboembolic event was recorded. There were 20 studies of statin vs control (87 634 randomised participants)[13-32] (of which one has published its findings subsequently[16]) and 7 trials of more intensive vs standard dose statin therapy (40 594 randomised participants)[33-39]. The characteristics of all the included trials are shown in the Table.

The primary analyses were restricted to the 21 trials that compared a statin with a control regimen (including the trial that generated the hypothesis) with 105 636 participants. In these trials, an episode of venous thromboembolic event occurred in 984 patients. Statin therapy did not reduce the risk of venous thromboembolic events significantly (464 [1.0 %] statin vs 520 [1.0%] control, OR=0.89 [95% CI 0.78 to 1.01]; p=0.07) and there was no evidence that the effect of statin therapy varied within these trials (heterogeneity X_{20}^2=23; p=0.29; Figure 2). Since the JUPITER trial generated the hypothesis being tested in the other 20 trials, inclusion of JUPITER trial could lead to a summary point estimate, confidence interval and p-value that are appreciably biased.[40, 41] Excluding this trial, however, did not materially change the overall results (430 [0.9 %] vs 460 [1.0%], OR 0.93; 95% CI 0.82 to 1.06; p=0.30; Figure 2).

Likewise, 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 (167 [0.8%] vs 152 [0.7%] respectively, OR 1.10; 95% CI 0.88 to 1.37; p=0.41) and there was no evidence that the effect varied within these trials (heterogeneity X_6^2=3.32; p=0.77; Figure 3).

Table. Summary of trials' characteristics

Study	Year of publication of main results	Mean follow-up (years)	Country/Region
Statin versus control regimen			
AFCAPS/TexCAPS (13)	1998	5,3	USA
LIPID (14)	1998	5,6	Australia, New Zealand
HPS (15)	2002	5,0	UK
PROSPER (16)	2002	3,2	Scotland, Ireland, Netherlands
ASCOT-LLA (17)	2003	3,2	Nordics and UK
ALERT (18)	2003	5,1	Multinational
CARDS (19)	2004	3,9	UK, Ireland
PREVEND IT (20)	2004	3,8	Netherlands
ALLIANCE (21)	2004	4,3	USA
4D (22)	2005	3,9	Germany
SALTIRE (23)	2005	2,2	UK
MEGA (24)	2006	5,3	Japan
ASPEN (25)	2006	4,3	Multinational
SPARCL (26)	2006	4,9	Multinational
CORONA (27)	2007	2,7	Multinational
Sola et al. (28)	2007	1,0	USA
JUPITER (7)	2008	1,9	Multinational
GISSI-HF (29)	2008	3,9	Italy
METEOR (30)	2009	2,0	Multinational
LEADe (31)	2010	1,5	Multinational
ASTRONOMER (32)	2010	3,5	Canada
More versus less intensive statin therapy			
ASAP (33)	2001	2,0	Netherlands
A-Z (34)	2004	2,0	Multinational
REVERSAL (35)	2004	1,5	USA
PROVE IT (36)	2004	2,0	Multinational
TNT (37)	2005	4,9	Multinational
IDEAL (38)	2005	4,8	Nordics, Netherlands, Iceland
SEARCH (39)	2010	6,7	UK

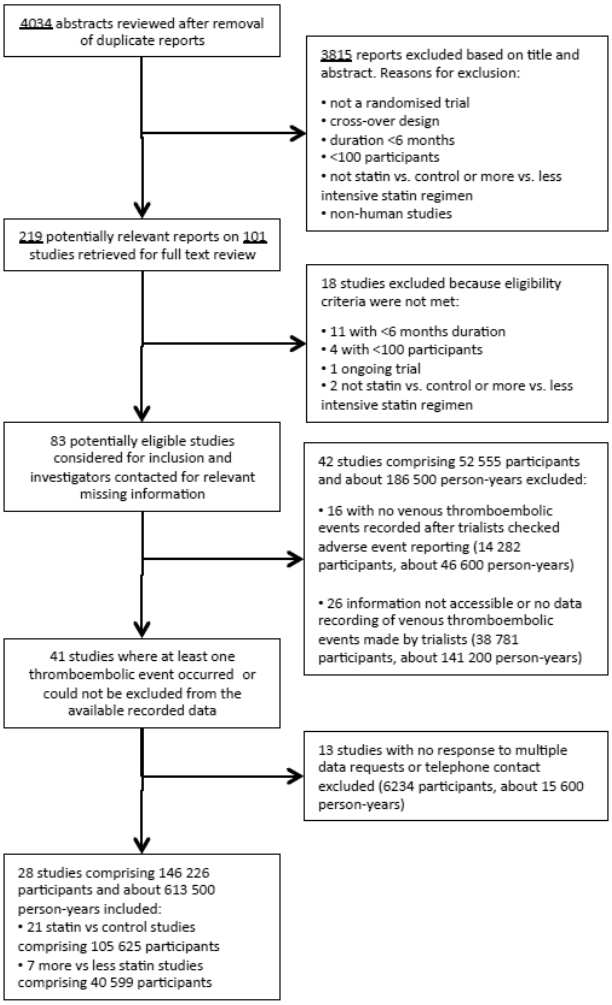
MI=myocardial infarction; CHD=coronary heart disease; CABG=coronary artery bypass graft surgery; TIA=transient ischaemic attack; CHF=chronic heart failure

A=Atorvastatin; L=Lovastatin; P=Pravastatin; R=Rosuvastatin; S=Simvastatin

† LDL-cholesterol differences are based on average differences between the two groups at 1 year (or the closest time to 1 year if 1 year data unavailable).

Treatment comparison		LDL-c difference† (mmol/L)	Population characteristics			
Intervention	Control Regimen		Main inclusion criteria	Total number of participants	Mean age (years)	Male (%)
L 20-40mg	Placebo	0,94	Primary prevention	6605	58	85
P 40mg	Placebo	1,03	History of MI or UA	9014	62	83
S 40mg	Placebo	1,29	Vascular disease or diabetes	20536	64	75
P 40mg	Placebo	1,04	Elderly with vascular disease or high risk	5699	75	47
A 10mg	Placebo	1,07	Hypertension plus other risk factor	10305	65	81
F 40mg	Placebo	0,84	Renal transplant recipients	2102	50	66
A 10mg	Placebo	1,14	Type 2 diabetes plus other risk factor	2838	62	68
P 40mg	Placebo	1,00	Microalbuminuric patients	864	51	65
A 10-80mg	Usual care	1,16	CHD	2442	61	82
A 20mg	Placebo	0,89	Diabetic hemodialysis patients	1255	66	54
A 80mg	Placebo	1,74	Calcific aortic stenosis	155	68	70
P 10-20mg	No treatment	0,67	Primary prevention	7832	58	30
A 10mg	Placebo	0,99	Type 2 diabetes	1864	61	66
A 80mg	Placebo	1,43	Stroke or TIA, no CHD	4731	63	60
R 10mg	Placebo	1,61	Ischemic heart failure	5011	73	76
A 20mg	Placebo	0,81	Nonischemic heart failure	108	54	33
R 20mg	Placebo	1,09	Primary prevention	17802	66	62
R 10mg	Placebo	0,92	CHF	4574	68	77
R 40mg	Placebo	1,79	Primary prevention	981	60	57
A 80mg	Placebo	0,30	Mild to moderate probable Alzheimer disease	640	74	48
R 40mg	Placebo	1,73	Mild to moderate aortic stenosis	269	58	61
A 80mg	S 40mg	0,62	Familial hypercholesterolaemia	325	48	40
S 80mg	S 20mg	0,30	Acute coronary syndrome	4497	61	75
A 80mg	P 40mg	0,97	>20% stenosis on routine coronary angiogram	657	56	72
A 80mg	P 40mg	0,65	Acute coronary syndrome	4162	58	78
A 80mg	A 10mg	0,62	Clinically evident CHD	10001	61	81
A 80mg	S 20mg	0,55	MI	8888	62	81
S 80mg	S 20mg	0,39	MI	12064	62	81

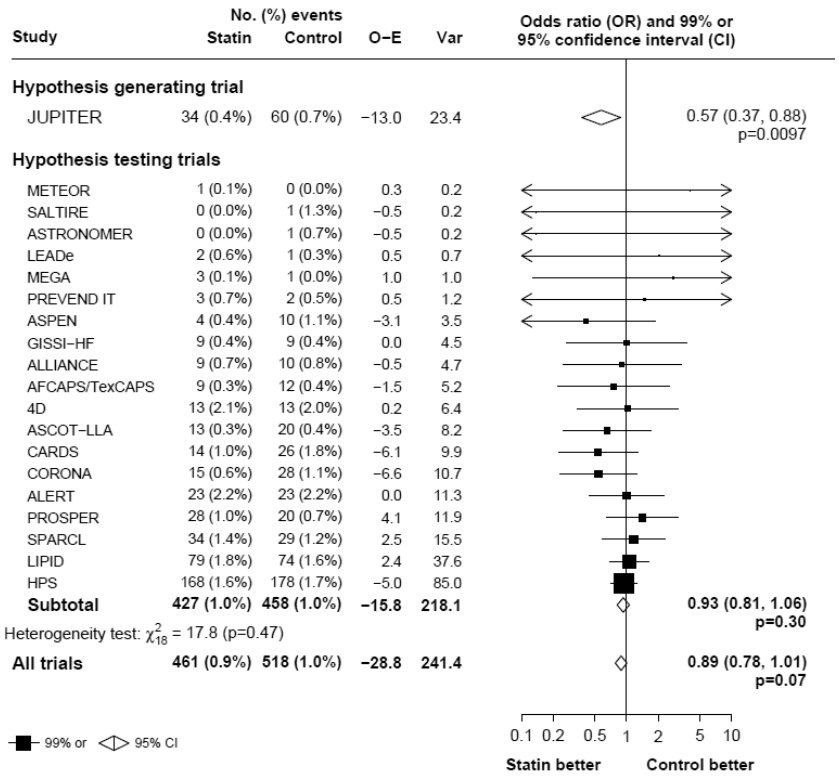
Figure 1. Flow-diagram of search retrieval process



To test a possible differential effect of statins (or higher dose statins) on pulmonary embolism and deep vein thrombosis, we tested for heterogeneity between these two outcomes. This showed no evidence that the effect of statin therapy differed by the type of outcome (X^2_1=0.3, p=0.56 for heterogeneity for statin vs control, and X^2_1=0.5, p=0.50 for heterogeneity for more intensive vs standard dose statin; Figure 4).

In a second subgroup analysis, we assessed the differential effect of type of statin in the 21 trials of statin vs control (Figure 5). While there was some suggestive evidence that the effect size differed between the trials by the type of statins used (X^2_5=10.8, p=0.06), the heterogeneity was largely explained by the hypothesis-generating JUPITER trial (X^2_5=6.0, p=0.30 after exclusion of JUPITER trial, webfigure 1).

Figure 2. Effect of statin therapy on venous thromboembolism



Test for difference between JUPITER and combined result from other trials: χ^2_1 = 4.9 (p = 0.026)

Figure 3. Effect of more intensive vs standard statin therapy on venous thromboembolism

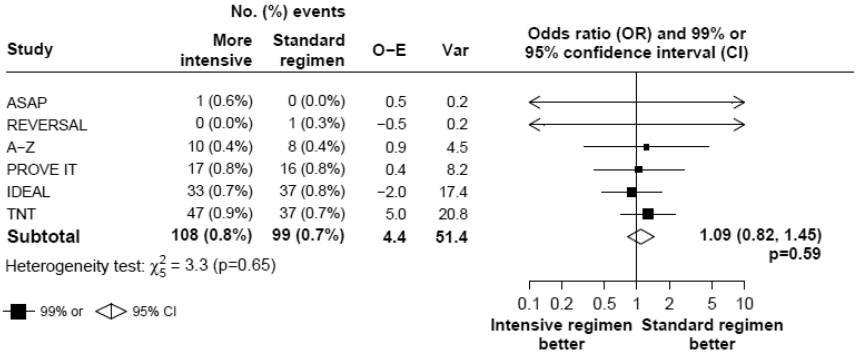


Figure 4. Effect of statin therapy on separate components of venous thromboembolism

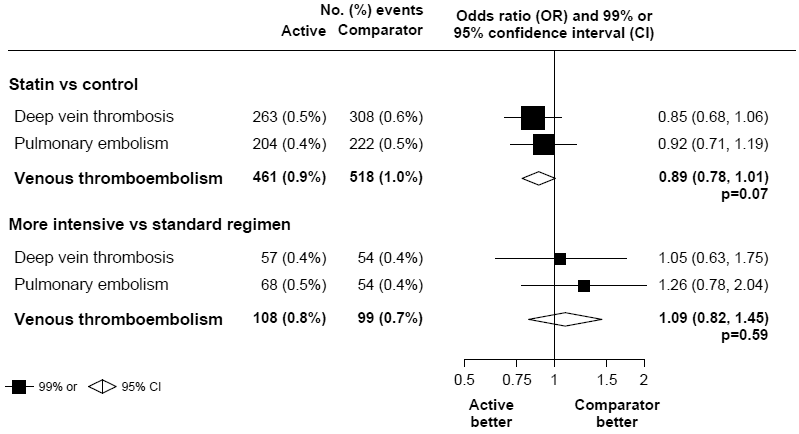
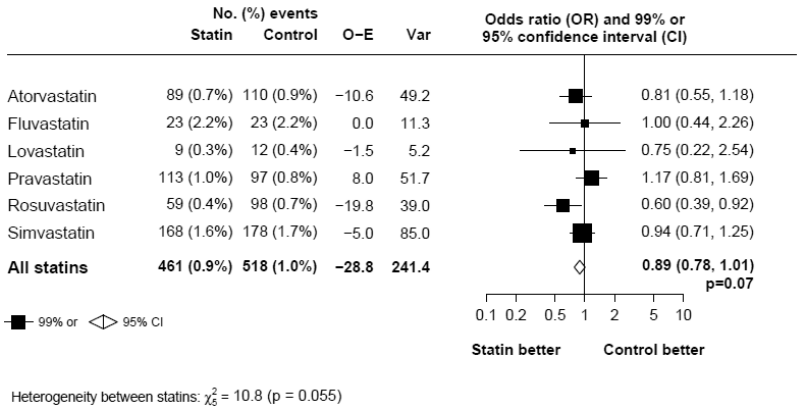
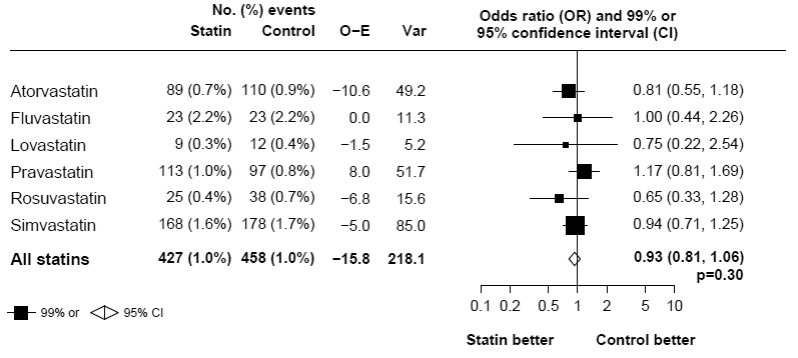


Figure 5. Effect of statin therapy on venous thromboembolism in trials of statin vs control, by type of **statin**



Heterogeneity between statins: $\chi^2_5 = 10.8$ (p = 0.055)

WebFigure 1. Effect of statin therapy on venous thromboembolism, in trials of statin vs control, by type of statin



Heterogeneity between statins: $\chi^2_5 = 6.0$ (p = 0.303)

EXCLUDING the hypothesis–generating JUPITER trial

DISCUSSION

In this study, we gathered information from over 140 000 participants in 21 randomised trials of statin therapy versus control and seven randomised trials of intensive versus standard dose statin therapy, which together involve more than ten times as many venous thromboembolic events as previously reported.[7] These findings do not support the suggestion that statins or higher dose statin therapy prevent venous thromboembolic events.

During recent years, statins have emerged as one of the most effective treatments to reduce the burden of 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.[7, 42, 43]

Venous and arterial thrombosis often co-occur[44, 45] and seem to share some common risk factors[46]. These findings together with experimental evidence revealing novel mechanisms for the beneficial effect of statins unrelated to their LDL cholesterol lowering effect [47-49] have raised hopes that statins may also protect against venous thromboembolic events. Contrasting previous suggestions from clinical studies[7, 50], however, we did not detect a significant protective effect of statins on venous thromboembolic events. This discrepancy may be due to the residual confounding and other inherent biases in the previous non-randomised studies[5, 6] and the presence of random error in the only randomised trial that tested this hypothesis[7]. Such random errors may lead to publication of strikingly positive findings, which are then often refuted in subsequent larger studies.[51]

The major strength of our study is the collection of a large number of mostly unpublished events that enables a reliable and independent assessment of even modest effect of statins on venous thromboembolic events. Nevertheless, we cannot entirely exclude a smaller (and arguably clinically less relevant) beneficial effect across the different populations included in the previous trials. Most events reported in the various included trials were collected from adverse event forms and were not pre-specified as study endpoints. Although such data capturing methods may have resulted in underestimation of the true number of events, they are unlikely to have introduced any bias because underreporting would be expected to have affected both study groups equally,[8, 52] and any random error due underreporting at the individual study level will have been compensated by pooling a large number of events from many studies. A further theoretical threat to the validity of pooled estimates is incomplete verification of events. However, this is also unlikely to have had any major impact on the overall outcomes for a condition where diagnostic pathway is less reliant on individual physicians judgement and intuition.[8, 16, 52]

It could be argued that even in the absence of any direct anti-thrombotic effects, statins may indirectly reduce venous thromboembolic events by reducing hospitalisation for arterial cardiovascular events as a risk factor for venous thromboembolic events. We did not have complete information about the circumstances in which venous thromboembolic events occurred to look at this subgroup of events directly. However, the absolute rate of occurrence of venous thromboembolic

events after cardiovascular events is likely to be small (for example six out of the total of 92 events in JUPITER[7]) and hence unlikely to have a material effect on the overall conclusions. If anything, such indirect effects would be expected to bias the findings away from null and would therefore support our conclusion. Finally, our findings do not exclude a beneficial effect in certain subgroups of people included in these trials. However, previous studies have been consistent in their conclusions about the lack of any differential effects between the investigated subgroups and we did not observe a statistically significant heterogeneity between the included studies.

In conclusion, in contrast to the unequivocal evidence for the beneficial effect of statins on atherosclerotic events, there is currently no compelling evidence that statin therapy or higher dose statin regimen prevent venous thromboembolic events.

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