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Is the lower risk of venous thromboembolism with statins related to low-density-lipoprotein reduction?

A network meta-analysis and meta-regression of randomised controlled trials

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ABSTRACT

Background and aims: Meta-analyses of randomised controlled trials (RCTs) have suggested a possible benefit of statin treatment on the risk of venous thromboembolism (VTE), with potential differences by type and dose of statins. We aimed to assess differences among statins and investigate the relationship between risk of VTE and reduction of LDL-cholesterol (LDL-c) levels.

Methods: We electronically searched through November 29, 2017 RCTs comparing a statin with either placebo or another statin, including 100 or more adult participants and lasting at least 24 weeks. Data on first VTE events and LDL-c were analysed with a network meta–analysis and a meta–regression.

Results: Thirty RCTs (159,058 participants; 1,431 events) were included, with 28 reporting LDL-c data. Network meta-analysis indicated a larger benefit for rosuvastatin compared to placebo and other statins; 50% of the effect of statins on VTE risk reduction, however, was explained by their different potencies in lowering LDL-c. The risk reduction in VTE was proportional to LDL-c decrease (37% relative lower risk per each 1 mmol/L reduction in LDL-c), without an apparent threshold. A reduction of 1 mmol/L in LDL-c would translate in 37 less VTE events per year in 100,000 people in UK, corresponding to 3,162 prevented episodes per year in people between 50-59 years.

Conclusions: In RCTs with statin treatment, the reduction of VTE risk was only partially related to LDL-c reduction and the benefit was larger than that observed for atherothrombotic risk. Further RCTs are warranted to clarify the relationship between statin, lipid modifications, and VTE risk.

Key words: Venous thromboembolism; statin; meta-analysis; LDL-cholesterol; clinical trials

INTRODUCTION

Statin treatment remains a cornerstone for the primary and secondary prevention of cardiovascular disease (CVD) [1]. Substantial evidence from individual participant data meta-analyses indicates a reduction of CVD risk proportional to the decrease in low-density-lipoprotein cholesterol (LDL-c) levels, either in randomised controlled trials (RCTs) of statin vs placebo or more intensive vs less intensive statin treatment [2, 3].

Beyond LDL-c reduction, other "pleiotropic" mechanisms could contribute to the beneficial effects of statins on atherosclerosis, including platelet inhibition, reduction of inflammation, and modulation of endothelial function [4, 5]. As there is only a partial overlap between arterial and venous thrombosis risk factors [6], the pleiotropic effects of statins could also explain the reduced risk of venous thromboembolism (VTE) observed in some RCTs. Available systematic reviews and study-level meta-analyses report divergent results on the efficacy of statin in the prevention of VTE and potential differences among different statins [7-9]. Moreover, the magnitude of the reduction of VTE risk related to LDL-c decrease remains to be established.

Very few RCTs have reported direct "head-to-head" comparisons between statins. When direct evidence is limited, network meta–analysis is considered the methodology of choice to estimate the comparative effectiveness of multiple treatments [10]. The method is based on the joint analysis of direct evidence (RCTs with treatments of interest) and indirect evidence (RCTs comparing treatments of interest with a common comparator). In this view, the objective of this research was three-fold. First, we aimed to clarify previous inconsistencies on a possible statin class effect by comparing statins using a network meta-analysis. Second, in light of the evidence of an inverse linear relationship between LDL-c reduction and risk of arterial thrombosis, we investigated the shape and quantified the strength of the association between risk of VTE and LDL-c reduction. Third, from a public health perspective, we contextualised our result estimating the absolute benefit of different statin treatments using contemporary epidemiological data of VTE in the UK.

MATERIALS AND METHODS

Search Strategy and Study Selection

We performed this analysis of a previously registered systematic review protocol following standard guidelines for conducting and reporting network meta-analysis (checklist in the Supplemental Material) [7, 11-13]. We searched PubMed, ISI Web of Science, and the Cochrane Library for RCTs published in any language between March 1st, 2012 and November 29th, 2017 and comparing statin vs placebo/no treatment or statin vs statin; this time frame allowed update of the meta-analyses by Kunutsor et al. and Rahimi and et al. (Supplemental Material Figure S1) [7, 8]. Key-words used for searches combined terms related to treatment (including specific statins) and outcomes (search strategy reported in the Supplemental Material). Two authors independently performed the literature search and RCTs (open or blinded trials) were deemed eligible for inclusion if they enrolled at least 100 adult participants and lasted 24 weeks or more and reported VTE events. Reference lists of selected studies, as well as previous systematic reviews and meta-analyses, were manually scanned for additional relevant data and studies.

Data Extraction and Quality Assessment

After the identification of the eligible studies, two authors independently extracted data using standardised pre–defined forms. Data were extracted on: first author name, clinical trial registration number, trial acronym, PubMed identification number, year of journal article publication, statin treatment and comparator, duration of follow-up, sample size, gender distribution, mean (or median) age, arm-specific number of participants and participants with event in patients who were randomised and received treatment, and baseline and follow-up LDL-c levels. When studies reported LDL-c data for different durations of follow-up, the longest was used. Study quality was assessed using the Cochrane risk of bias tool [14].

Data Synthesis and Analysis

We undertook a network meta–analysis within a frequentist model using the method of multivariate meta–analysis and assuming that all treatment contrasts have the same heterogeneity variance [15, 16]; we assessed consistency between direct and indirect evidence by using the 'design by treatment' interaction model and expected that participants of the included RCTs could be randomly allocated to any of the treatments being compared [17]. We summarised the available evidence with a network diagram [18], reported characteristics and summary data of included RCTs in tables, and plotted the estimated odds ratios (ORs) vs a common comparator (placebo) in a forest plot. If one arm reported zero events, ORs were calculated using the "opposite-arm" continuity correction to account for the imbalance in the number of participants between the two arms [19]. Comparisons among statins were reported in tables, as previously advocated [20], and ranking probabilities for each statins were displayed in bar plots. Lastly, we evaluated the association between study size and result with a comparison-adjusted funnel plot [18].

We calculated rates of VTE events for each arm of the included RCTs dividing the number of VTE events (numerator) by the product of mean/median follow-up and number of participants (i.e., person-years; denominator). We further investigated the relationship between VTE risk and LDL-c reduction with a univariate meta-regression using the natural log of study-specific odds ratio as dependent variable and the between-arm percentage reduction of LDL-c as the independent variable [21, 22]. We first estimated within-arm percentage difference of LDL-c comparing end of follow-up vs baseline (i.e., $100\frac{\text{Final value}-\text{Baseline value}}{\text{Baseline value}}$); then, the difference of the percentages between the two arms (statin vs placebo or more intensive vs less intensive statin) was used as independent variable. We opted to calculate percentage (i.e., relative) rather than absolute differences to account for potential imbalance of LDL-c levels at baseline. Given the possible non-linearity of the association, we also modelled the independent variable using cubic splines with 4 knots (at 5, 35, 65, and 95 percentile of its distribution)[23] and performed a weighted least-squares linear regression being the weight the inverse of study-specific variance; the two models (linear vs

non-linear) were then compared using the Akaike information criterion. Finally, we calculated the corresponding risk (CR) of VTE per 100,000 person-years (assuming a causal relationship between statin treatments and incident VTE) using the formula $\mathrm{CR} = 10^5 \frac{\mathrm{OR}*\mathrm{ACR}}{1-\mathrm{ACR}+(\mathrm{OR}*\mathrm{ACR})}$ [24]; ORs for 20% to 60% reduction of LDL-c were derived from the current meta-regression while the assumed control risk (ACR) for first unprovoked VTE was retrieved from the analysis of primary care patients in UK (Clinical Practice Research Datalink) [25]. CR and ACR data allowed the estimation of potentially avoidable number of VTE events associated with statin treatment and, along with data on mid-year population by age groups in UK in 2015 [26], to quantify avoidable events in UK. For the estimations of potential effects at a population level, we first confirmed with meta-regressions that the risk reduction of VTE was homogenous across different levels of age and sex; similarly, we also assessed whether the reduction of VTE risk differed according to the prevalence of CVD in RCTs participants (only primary prevention participants, only secondary prevention, both).

Stata 14.1 (Stata Corp, College Station, TX, USA) was used for all analyses; we considered $p<0.05$ as statistically significant.

RESULTS

Characteristics of Included Studies

After duplicates exclusion and selection of articles by title and abstract, 380 recently published articles were found from the update search between March 1st, 2012 and November 29th, 2017 and none fulfilled the inclusion criteria. Of the 30 RCTs published before March 1st, 2012, information on LDL-c was not available in five RCTs; a manual search of references allowed extraction of LDL-c information from three other reports [27-29], leaving 28 out of 30 RCTs with available LDL-c data (Figure S1).

The characteristics and the references of the included RCTs are reported in Table 1 and Supplemental Material Table S1 and S2: studies were published between 1998 and 2016, enrolled 159,058 (range, 108 to 20,536) participants with 1,431 (range, 1 to 346) incident VTE episodes, had a median follow-up of 3.9 (range, 1 to 6.7) years with VTE rates ranging from 0 to 55.6 per 1000 person-years (Table S2); baseline age weighted mean was 63.6 (range, 48 to 75) years and 70.1 (range, 48 to 75) % were men (Figure S2). For the 28 RCTs with available information on cholesterol, the baseline LDL-c weighted mean was 3.33 mmol/L (range, 2.51 to 8.33). Twenty-three RCTs compared a statin vs placebo and seven compared two different statins. Six different statins were investigated (four doses of atorvastatin; three of rosuvastatin and simvastatin; two of pravastatin; and one of fluvastatin and lovastatin) reporting on overall 17 different pairwise comparisons.

The risk of bias was deemed low, high, and unclear in 65.6%, 3.9%, and 30.5% of the cases, respectively (Table S3); high or unclear domain-specific bias was lowest for “selective reporting” (6.7%) and highest for “incomplete outcome data” (93.3%).

Network Meta-Analysis and Meta-Regression

The network of evidence is shown in Figure 1 while differences for each statin vs placebo and cross comparisons among statins in Figure S3 and in Table 2, respectively. When compared to placebo, the results of the network meta-analysis showed a lower risk of VTE for both rosuvastatin 10mg (OR

0.56; 95% confidence interval (CI): 0.37 to 0.83) and 20mg (0.57; 0.37 to 0.86); and for atorvastatin 10mg (0.66; 0.47 to 0.94) (Figure S3). When compared against each other, rosuvastatin 10mg and 20mg showed a greater reduction of the risk of VTE vs pravastatin 40mg, atorvastatin 80mg, and simvastatin 40mg (Table 2): ORs of VTE were 0.50 (0.31 to 0.80) and 0.50 (0.31 to 0.82) for rosuvastatin 10mg and 20mg, respectively, when compared to pravastatin 40mg; 0.55 (0.33 to 0.93) and 0.56 (0.33 to 0.96) when compared to atorvastatin 80mg; and 0.59 (0.38 to 0.93) and 0.60 (0.38 to 0.96) when compared to simvastatin 40mg. The risk was also lower for rosuvastatin 40mg when compared to simvastatin 20mg (OR 0.49; 0.24 to 1.00); and for atorvastatin 10mg when compared to both atorvastatin 80mg (0.66; 0.46 to 0.93) and pravastatin 40mg (0.59; 0.39 to 0.89). The ranking probabilities showed a higher probability for rosuvastatin at a dose of 40mg to be the best treatment (39.6% to rank first), followed by the lower doses of 10mg (18.2%) and 20mg (16.2%) (Figure S4 and Figure S5). There was no evidence of inconsistency in the network of comparisons (p=0.538) and the visual inspection of the comparison-adjusted funnel plot did not suggest publication bias (Figure S6).

The meta-regression analyses showed no different reductions in VTE risk with statin treatments comparing men and women (p=0.740) or across mean ages of included participants (p=0.428) (Figure S7). Conversely, there was an inverse linear relationship between the risk of VTE and the LDL-c reduction (Figure 2). Change in LDL-c levels explained 51.2% in the VTE risk reduction, with an estimated 14.4% (95% confidence interval (CI): 0.2, 26.6; p=0.047) lower risk of VTE per each 10% reduction of LDL-c, corresponding to 37.3% (95% CI: 0.6, 60.4) per 1 mmol/L (i.e., 30% reduction of LDL-c in this meta-analysis). These estimates indicate an absolute benefit in the UK population ranging from 14 less cases of first VTE events per 100,000 person per year in subjects between 30 to 39 years with a 20% reduction of LDL-c to 199 less cases in subjects between 70-79 years with 60% LDL-c reduction; these figures translate in 1217 and 9707 fewer VTE cases per year, respectively (Figure 3).

AIC values did not suggest a non-linear relationship between LDL-c change and risk of VTE (21.9 for the linear vs 24.6 for the non-linear model, with lower values indicating better model) and, accounting for LDL-c reduction, there was no difference in the reduction of VTE risk across RCTs including only participants in primary CVD prevention, only secondary prevention, or both (p=0.109; Table S1).

DISCUSSION

In this analysis, we found differences among statins in the prevention of VTE, with a greater efficacy for rosuvastatin at any dose (10mg, 20mg, and 40mg) compared to other statins. Such differences, however, were mainly explained by dissimilarity among statins in their potency/intensity to reduce LDL-c. We estimated that 30% reduction in LDL-c, which equates to 1 mmol/L in our meta-analysis, would reduce the risk of VTE on mean by 37%. This beneficial effect seemed to be continuous, without any apparent threshold.

Added value to previous meta-analysis on the same topic

Systematic investigations of both observational and RCTs have not clarified whether the risk reduction of VTE with statins is a class effect [7, 8, 30]. While differences among statins for the secondary prevention of venous thromboembolism in observational studies have not been investigated [30, 31] or demonstrated [32], on the basis of 22 RCTs comparing statins vs placebo Rahimi et al. concluded that there was no good evidence of a variation by specific statin treatment [8]. More recently, Kunutsor et al. suggested a larger benefit for rosuvastatin compared to other statins combining data from 23 statin vs placebo in RCTs [7]. Both analyses, however, did not include "head-to-head" RCTs, given the difficulties of pooling together studies investigating statin vs placebo and statin vs statin with a standard pairwise meta-analysis, which can compare only two interventions at a time. In the last years, the introduction of NMA is allowing researchers to combine information from RCTs reporting different pairwise comparisons and rank competing interventions combining direct and indirect evidence. NMA approach has been adopted within the technology appraisal from multiple countries and is considered the "gold standard" to compare the complete set of treatments [33]. The result of this NMA evidenced some differences among statins, indicating that rosuvastatin at any dose has the larger probability to reduce the risk of VTE compared to other statins. From this perspective, our findings corroborate and reinforce the differences observed in the previous meta-analysis while adding also evidence from "head-to-head" RCTs [7].

In the last decades, the importance of cholesterol in determining cardiovascular risk and the pivotal role of lowering cholesterol with statins to reduce cardiovascular events has been clearly demonstrated. In observational studies, populations with low LDL-c levels experience a lower risk of cardiovascular events and most cardiovascular risk prediction models require information on cholesterol levels [34]. At the same time, results from multiple, large international RCTs have undoubtedly demonstrated that lowering LDL-c with statins reduces the risk of cardiovascular disease [1]. In particular, insights into the relationship between LDL-c, statins, and cardiovascular atherosclerotic events has emerged from individual participant data meta-analyses of RCTs, indicating a strong, linear inverse association between LDL-c reduction and risk of atherothrombosis. The Cholesterol Treatment Trialists' Collaborators (CTT) meta-analysis reported a 21% relative risk reduction of major vascular atherothrombotic events per 1 mmol/L reduction of LDL-c combining statin vs placebo RCTs [2]; a similar estimate was found combining RCTs with more intensive vs less intensive statin treatment (26% risk reduction per 1mmol/L lower LDL-c) [3]. In a recent review, however, Gaertner et al. underlined that the putative preventive effects of statins on VTE appear to be independent of the LDL-c reduction highlighting, at the same time, that a dose-response relationship has not been demonstrated [35]. Our study indicates a relative risk reduction of 37% per 1 mmol/L of LDL-c, which is higher than estimates for atherothrombotic events. Such higher benefit on venous compared to arterial thrombosis, along with the findings that around 50% of the statin effects on the risk VTE is explained by LDL-c reduction, would underline that pleiotropic mechanisms play an important role in the prevention of VTE beyond LDL-c reduction.

Potential mechanisms related to VTE risk reduction with statins

Pre-clinical and clinical studies in the last two decades have investigated the effects of statins on multiple mechanisms of venous thrombosis. The three main pathophysiological determinants of VTE are classically considered to be blood stasis, hypercoagulability, and endothelial dysfunction, and two of these factors are directly modulated by statin therapy. In fact, statins have been shown to

influence the coagulation process via different pathways, including a reduced thrombin formation,[36] inhibition of plasminogen activator inhibitor 1 synthesis [37], enhanced fibrinolysis [38], and reducing platelet activity [39]. In this circumstance, the "anti-platelet" activity of statin could be particularly relevant because individual-participant data from the two largest placebo-controlled RCTs investigating aspirin and VTE have shown a 32% relative reduction of a recurrent VTE after a first unprovoked event in patients randomised to aspirin [40]. Statins have also effects on the endothelial function, increasing the expression of thrombomodulin, the synthesis of nitric oxide and prostacyclin, and reducing oxidative stress via a downregulation of NADPH oxidase expression [39]. These anti-coagulative, anti-platelet, and endothelial mechanisms, along with anti-inflammatory properties, could explain the larger effect of statins for venous as compared to arterial thrombosis. Lastly, it should be also noted that an observational retrospective analysis did not find a reduced risk of VTE events in patients treated with lipid-lowering agents other than statins [41-43], further suggesting that pleiotropic mechanisms could contribute to the beneficial effects of statins on the risk of venous thrombosis.

Strengths and limitations

Our studies has several strengths. Compared to previous meta-analyses, we used a NMA approach combining all available evidence in a single analysis to compare multiple treatments and estimate, for each of them, the probability to be the best for the reduction of VTE risk. We also performed a meta-regression to investigate the shape of the association (linear vs non-linear) and clarify whether potential differences observed in the NMA could be explained by dissimilar potencies of statins; for this analysis, we included 28 studies compared to the 23 reported in a previous analysis [8], thus enhancing the statistical power. Lastly, we quantified the public health implications of our results using updated data on the incidence of VTE in UK. Some limitations should also be considered while interpreting these findings. First, available data did not allow stratification of VTE events into provoked or unprovoked and very sparse information specifically on pulmonary embolism and deep

vein thrombosis were reported. Second, information on LDL-c was not available for all studies and, in some circumstances, was reported either for a different follow-up compared to the end of the study or for a subsample of the included participants. However, when multiple follow-up data were available, we selected the longest. Third, in the estimations of the potential effects of statin at population level, we assumed the risk reduction to be homogenous across different levels of age and sex, in line with the results of our meta-regressions (no effects of age and sex) and with those of the CTT collaboration for atherothrombotic events [2, 3, 44]. Moreover, we considered UK because we found published data on the epidemiology of VTE for this country, although our estimates could be similarly applied to other countries with available data on VTE epidemiology. Fourth, limitations of the analytical procedures should also be acknowledged. Heterogeneity of studies is a common drawback for both NMAs and meta-regressions [22, 45]. Some characteristics (participants enrolled, duration of follow-up, background therapies, and quality of studies) differed among included RCTs: this could justify both differences in the incidence rates (i.e., absolute risk) of VTE across RCTs and the wide confidence intervals observed in some NMA comparisons and in the meta-regression estimate. However, we did not find inconsistency in the network of comparisons. Furthermore, although the original studies were randomised and there is a substantial clinical and pre-clinical evidence on the lowering effects of statins on LDL-c, the relationship between LDL-c reduction and VTE in the meta-regression is across trials and therefore observational [22]. Nonetheless, LDL-c could at least be considered a marker of the beneficial effects of statins on VTE risk reduction. Fifth, the direction of the association between a biomarker and an outcome could be different when explored at individual level (i.e., within a RCT) or across multiple RCTs (“ecological bias”) [22]. Lastly, the results of the NMA indicated a larger reduction of VTE risk comparing atorvastatin 10mg vs atorvastatin 80mg, in apparent contrast with the meta-regression finding. There are two possible reasons. First, it is not uncommon in meta-analyses to obtain an overall estimate which is in contrast with one (or more) single study estimate, particularly in the presence of heterogeneity across studies. Moreover, only around 50% of the statin effect is explained by LDL-c reduction. Second, it

was not possible to account for change in LDL-c reduction in the NMA because of the sparsity of the network (there were only single comparisons for fluvastatin, lovastatin, and rosuvastatin 20mg).

Conclusions

Our results would indicate that differences among statins and their doses in the prevention of VTE are related to their different potency in reducing LDL-c, suggesting that the relationship between LDL-c decrease and the risk of vascular events could hold not only for arterial but also venous thrombosis. The risk reduction for the same decrease of LDL-c, however, was larger for VTE compared to major atherosclerotic events, which would postulate that mechanisms other than LDL-c reduction could be involved in the prevention of VTE with statin treatment.

Venous thromboembolism remains a significant clinical and public health problem. Recent data indicate an overall incidence, in the general population, of 107 first non-cancer-related VTE episodes per 100,000 people per year and a 7% mortality one year after the event [25, 46]. Once VTEs occur, anticoagulants represent the cornerstone for treatment; there are, however, no strategies for the primary prevention of unprovoked VTE in the general population and the optimal risk/benefit preventive approach still needs to be defined. Given the increasing prevalence of multimorbid elderly patients at an increased risk of VTE [25], statin treatment could be an effective low-cost option to reduce the risk of first VTE events: at a cost of one more case of myopathy, 10-20 more cases of diabetes, and 1-2 more cases of haemorrhagic stroke per 10,000 people per year with a 50% reduction of LDL-c [1], the same reduction would also result in 5-10 less cases of VTE in people between 50-70 years.

These results of this analysis should further encourage to design appropriate RCTs (with VTE as primary outcome) and to perform collaborative individual-participant data meta-analysis aiming: to shed light on the efficacy and safety of statins in the prevention of venous events; to clarify the nature, shape, and strength of the association with LDL-c reduction in better detail; to investigate the heterogeneity of effects according to relevant clinical characteristics and identify patients whose

benefit/risk is optimal (stratified medicine); and to estimate the absolute benefit and risk. Answers to these questions are relevant, given the likely increase of VTE incidence in the future, the absence of a defined strategy to prevent the risk of first unprovoked VTE events, and the excellent benefit/risk profile and the low cost of available statins.

Competing interests

SS has received honoraria for speaking at meetings and serving on Advisory Boards for Novartis, Novo Nordisk, Janssen, MSD, Lilly, and Boehringer Ingelheim.

MJD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi–Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi–Aventis and Lilly.

KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi–Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi–Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme.

FZ and SKK have nothing to disclose.

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Author Contribution

KK, FZ, SKK: study idea and design; FZ, SKK, SS: literature search and data extraction; FZ: data analysis; FZ: first draft; all Authors: study critical revision and manuscript draft. All authors provided final approval of the version to publish. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data access and sharing

Databases and statistical codes are available on request from the corresponding author (FZ).

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Figure 1: Network map

Legend: Nodes represent the competing treatments and edges the available direct comparisons between pairs of treatments. Nodes and edges are weighted according to the number of studies involved in each treatment and comparison, respectively

* Doses were 20mg and 40mg for each half of participants in the randomised controlled trial

Figure 2: Association between risk of venous thromboembolism and LDL-c reduction

Legend: The plotted data show the relationship between risk of venous thromboembolism and LDL-c reduction. The dotted line indicates the predicted correlation and the grey area the 95% confidence interval (CI). Each circle represents a randomised controlled trial and its size is proportional to the inverse of study variance. The risk of venous thromboembolism was reduced by 37.3% (95% CI: 0.6, 60.4) per each 30% (i.e., 1 mmol/L) reduction of LDL-c; Adjusted R^2=51.2%

Figure 3: Number of avoided venous thromboembolism events associated with LDL-c reduction with statins

Legend: Age groups and LDL-c reductions were selected to be consistent with values reported in included randomised controlled trials. Age-specific data for venous thromboembolism incidence and mid-year populations were obtained from CPRD [25] and ONS [26], respectively.

Table 1: Characteristics of the included studies

Study	Publication Year	Arm 1			Arm 2			Follow-up (years)	Males (%)	Diabetes (%)	Age[d] (years)	Available LDL-c data
		Intervention	Participants	Events	Intervention	Participants	Events					
ASCOT-LLA	2003	Atorvastatin 10mg	5168	13	Placebo	5137	20	3.2	65	25	81	✓
CARDS	2004	Atorvastatin 10mg	1428	14	Placebo	1410	26	3.9	62	100	68	✓
ASPEN	2006	Atorvastatin 10mg	948	4	Placebo	916	10	4.3	61	100	66	✓
LORD	2010	Atorvastatin 10mg	64	1	Placebo	68	1	2.5	62	8	65	✓
4D	2005	Atorvastatin 20mg	619	13	Placebo	636	13	3.9	66	100	54	✓
Sola et al.	2006	Atorvastatin 20mg	54	3	Placebo	54	2	1.0	54	0	33	✓
ALLIANCE	2004	Atorvastatin 40mg[a]	1217	9	Placebo	1225	10	4.3	61	22	82	✓
SALTIRE	2005	Atorvastatin 80mg	77	0	Placebo	78	1	2.2	68	5	70	✓
SPARCL	2006	Atorvastatin 80mg	2365	34	Placebo	2366	29	4.9	63	17	60	✓
LEADe	2010	Atorvastatin 80mg	314	2	Placebo	326	1	1.5	74	-	48	✓
TNT	2005	Atorvastatin 80mg	4995	47	Atorvastatin 10mg	5006	37	4.9	61	15	81	✓
PROVE IT–TIMI 22	2004	Atorvastatin 80mg	2099	17	Pravastatin 40mg	2063	16	2.0	58	18	78	✓
REVERSAL	2004	Atorvastatin 80mg	328	0	Pravastatin 40mg	329	1	1.5	56	19	72	✓
IDEAL	2005	Atorvastatin 80mg	4439	33	Simvastatin 20mg	4449	37	4.8	62	12	81	✓
ASAP	2001	Atorvastatin 80mg	160	1	Simvastatin 40mg	165	0	2.0	48	-	39	✓
ALERT	2003-4	Fluvastatin 40mg	1050	23	Placebo	1052	23	5.1	50	19	66	✓
AFCAPS/TexCAPS	1998	Lovastatin 20mg[b]	3304	9	Placebo	3301	12	5.3	58	4	85	✓
MEGA	2006	Pravastatin 10mg[c]	3866	3	Placebo	3966	1	5.3	58	21	30	✓
LIPID	1998	Pravastatin 40mg	4512	79	Placebo	4502	74	5.6	62	9	83	✓
PREVEND IT	2004	Pravastatin 40mg	433	3	Placebo	431	2	3.8	51	3	65	✓
PROSPER	2002-11	Pravastatin 40mg	2834	28	Placebo	2865	20	3.2	75	11	47	✓
CORONA	2007	Rosuvastatin 10mg	2514	15	Placebo	2497	28	2.7	73	30	76	✓
GISSI-HF	2008	Rosuvastatin 10mg	2285	9	Placebo	2289	9	3.9	68	26	77	✓
HOPE-3	2016	Rosuvastatin 10mg	6361	14	Placebo	6344	31	5.6	66	6	54	✓
JUPITER	2008-9	Rosuvastatin 20mg	8901	34	Placebo	8901	60	1.9	66	0	62	✓
METEOR	2007	Rosuvastatin 40mg	700	1	Placebo	281	0	2.0	60	0	57	✓
ASTRONOMER	2010	Rosuvastatin 40mg	134	0	Placebo	135	1	3.5	58	0	61	✓
HPS	2002	Simvastatin 40mg	10269	168	Placebo	10267	178	5.0	64	36	75	×
A-Z	2004	Simvastatin 80mg	2265	10	Simvastatin 20mg	2232	8	2.0	61	24	76	✓
SEARCH	2010	Simvastatin 80mg	6031	90	Simvastatin 20mg	6033	103	6.7	64	37	83	×

References are reported in Table S1 in the supplementary material

LDL-c = Low-density lipoprotein cholesterol

[a] Median dose
[b] Doses were 20mg and 40mg for each half of participants in the RCT
[c] Mean dose
[d] Mean or median

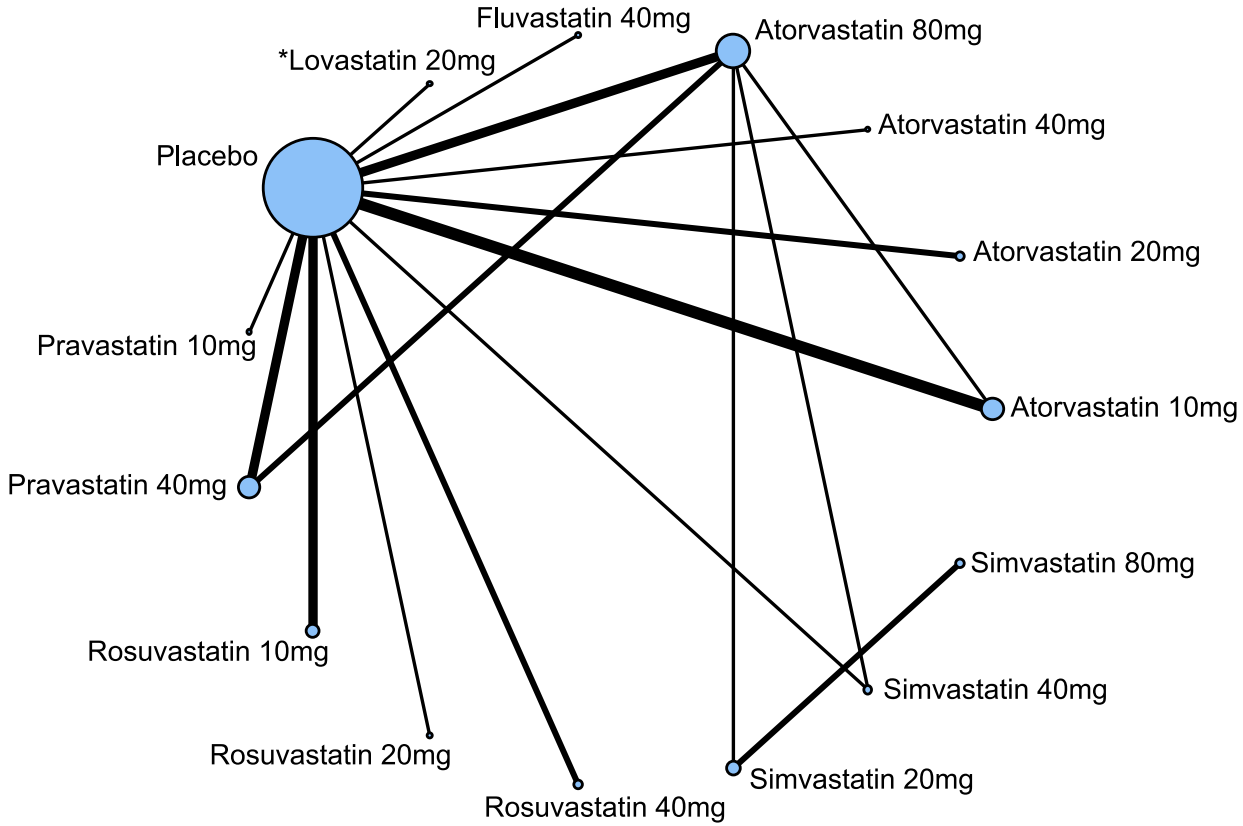
Table 2: Cross-comparisons of individual statins for risk of venous thromboembolism

												Simvastatin 80mg
											Simvastatin 40mg	1.09 (0.55,2.13)
										Simvastatin 20mg	0.83 (0.45,1.53)	0.90 (0.68,1.18)
									Rosuvastatin 40mg	1.68 (0.11,25.09)	1.39 (0.10,19.68)	1.51 (0.10,22.85)
								Rosuvastatin 20mg	1.20 (0.08,17.40)	2.01 (0.98,4.10)	**1.66 (1.04,2.66)**	1.80 (0.84,3.88)
							Rosuvastatin 10mg	1.01 (0.56,1.81)	1.21 (0.08,17.54)	**2.03 (1.00,4.10)**	**1.68 (1.07,2.65)**	1.82 (0.86,3.88)
						Pravastatin 40mg	**0.50 (0.31,0.80)**	**0.50 (0.31,0.82)**	0.60 (0.04,8.53)	1.00 (0.55,1.84)	0.83 (0.59,1.16)	0.90 (0.46,1.76)
					Pravastatin 10mg	0.37 (0.04,3.58)	0.18 (0.02,1.81)	0.18 (0.02,1.83)	0.22 (0.01,7.13)	0.37 (0.04,3.81)	0.30 (0.03,2.96)	0.33 (0.03,3.47)
				Lovastatin 20mg[a]	4.11 (0.36,46.42)	1.51 (0.61,3.72)	0.75 (0.29,1.94)	0.75 (0.29,1.98)	0.90 (0.06,14.58)	1.51 (0.53,4.29)	1.25 (0.51,3.06)	1.36 (0.46,3.99)
			Fluvastatin 40mg	0.75 (0.26,2.12)	3.07 (0.30,31.83)	1.13 (0.59,2.13)	0.56 (0.27,1.13)	0.56 (0.27,1.16)	0.67 (0.05,10.11)	1.13 (0.50,2.57)	0.94 (0.50,1.74)	1.02 (0.43,2.42)
			Atorvastatin 80mg	0.99 (0.50,1.94)	0.74 (0.29,1.87)	3.04 (0.31,29.98)	1.11 (0.76,1.64)	**0.55 (0.33,0.93)**	**0.56 (0.33,0.96)**	0.67 (0.05,9.59)	1.12 (0.70,1.79)	0.93 (0.62,1.38)	1.01 (0.58,1.73)
		Atorvastatin 40mg	1.12 (0.43,2.93)	1.11 (0.38,3.25)	0.83 (0.24,2.89)	3.40 (0.30,38.93)	1.25 (0.49,3.19)	0.62 (0.23,1.66)	0.62 (0.23,1.69)	0.75 (0.05,12.21)	1.25 (0.43,3.66)	1.04 (0.41,2.62)	1.12 (0.37,3.40)
	Atorvastatin 20mg	0.83 (0.26,2.62)	0.93 (0.42,2.04)	0.92 (0.36,2.31)	0.69 (0.22,2.11)	2.82 (0.26,30.27)	1.03 (0.48,2.21)	0.51 (0.23,1.16)	0.52 (0.23,1.19)	0.62 (0.04,9.57)	1.04 (0.41,2.60)	0.86 (0.41,1.81)	0.93 (0.36,2.43)
Atorvastatin 10mg	1.64 (0.74,3.64)	1.36 (0.52,3.59)	**1.52 (1.07,2.16)**	1.51 (0.76,2.98)	1.13 (0.44,2.87)	4.63 (0.47,45.78)	**1.70 (1.12,2.58)**	0.84 (0.49,1.43)	0.85 (0.49,1.47)	1.02 (0.07,14.64)	1.71 (0.95,3.07)	1.41 (0.94,2.13)	1.53 (0.80,2.93)

Comparisons are shown column vs row, i.e. Rosuvastatin 10mg is associated with an Odds Ratio for VTE of 0.55 compared to Atorvastatin 80mg [or, equivalently, Atorvastatin 80mg is associated with an Odds Ratio of 1.82 (=1/0.55) compared to Rosuvastatin 10mg]. Statistically significant differences are in bold.

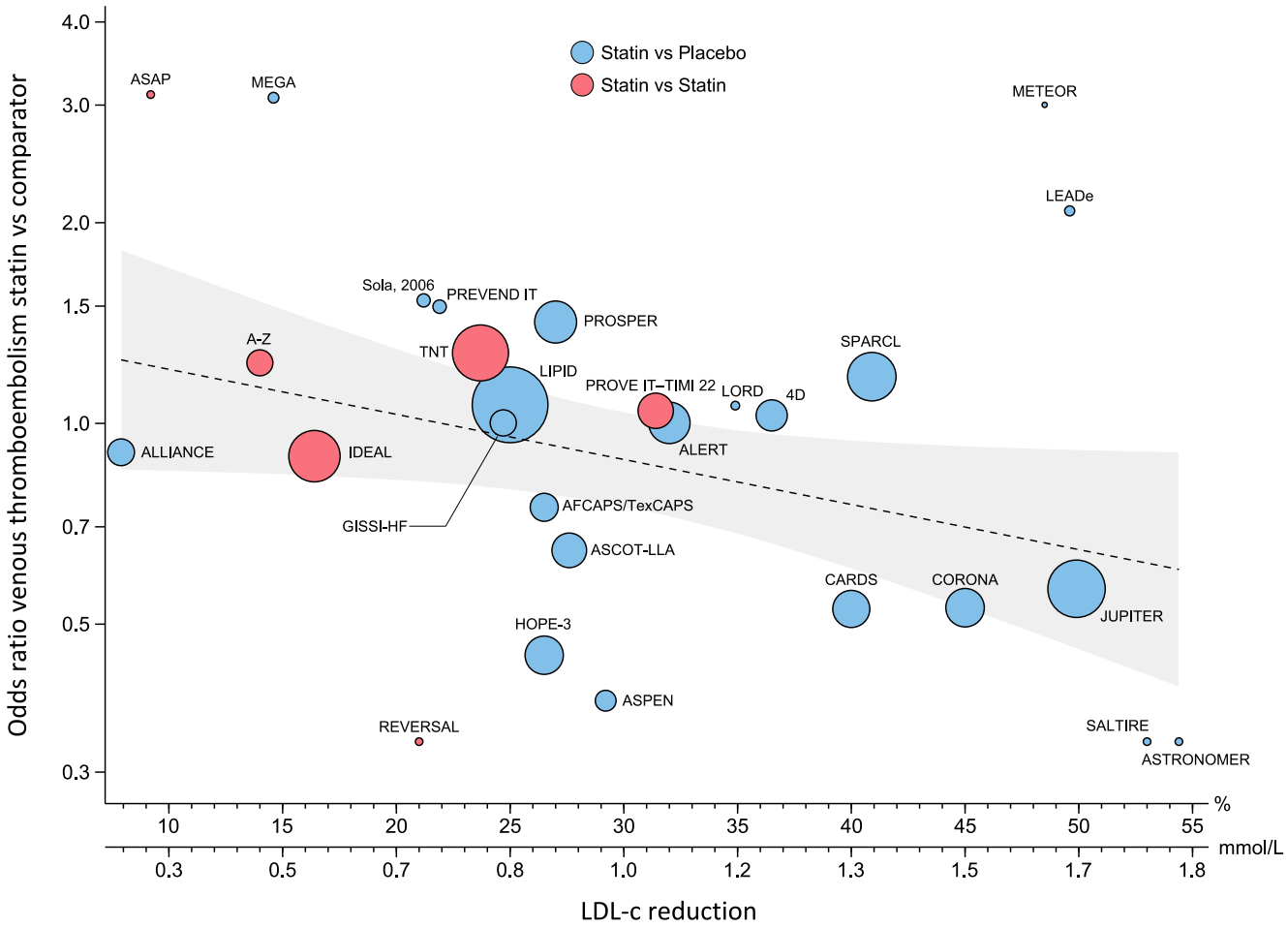
[a] Doses were 20mg and 40mg for each half of participants in the RCT

Figure 1: Network map



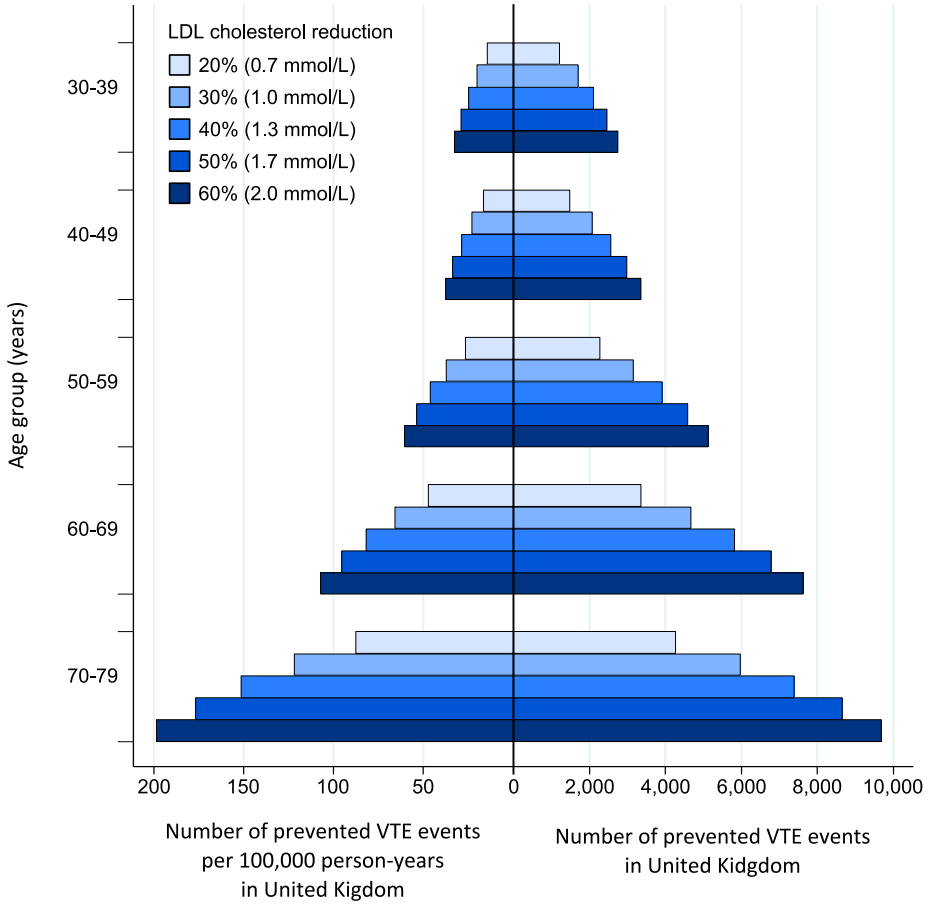
Nodes represent the competing treatments and edges the available direct comparisons between pairs of treatments. Nodes and edges are weighted according to the number of studies involved in each treatment and comparison, respectively. * Doses were 20mg and 40mg for each half of participants in the randomised controlled trial

Figure 2: Association between risk of venous thromboembolism and LDL-c reduction



The plotted data show the relationship between risk of venous thromboembolism and LDL-c reduction. The dotted line indicates the predicted correlation and the grey area the 95% confidence interval (CI). Each circle represents a randomised controlled trial and its size is proportional to the inverse of study variance. The risk of venous thromboembolism was reduced by 37.3% (95% CI: 0.6, 60.4) per each 30% (i.e., 1 mmol/L) reduction of LDL-c; Adjusted R^2=51.2%

Figure 3: Number of avoided venous thromboembolism events associated with LDL-c reduction with statins



Age groups and LDL-c reductions were selected to be consistent with values reported in included randomised controlled trials. Age-specific data for venous thromboembolism incidence and mid-year populations were obtained from CPRD[25] and ONS[26], respectively.