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Risk of Venous Thromboembolism with Statins: Evidence Gathered via a Network Meta-analysis

Oğuzhan Birdal[1], Mehmet Saygı[2], Remziye Doğan[2], Ozan Tezen[3], Ali Karagöz[4], İbrahim Halil Tanboğa[2,5]

[1]Department of Cardiology, Atatürk University Faculty of Medicine, Erzurum, Turkey
[2]Clinic of Cardiology, Hisar Intercontinental Hospital, İstanbul, Turkey
[3]Clinic of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training Hospital, İstanbul, Turkey
[4]Clinic of Cardiology, Koşuyolu Heart Hospital, İstanbul, Turkey
[5]Department of Cardiology and Biostatistics, Nişantaşı University Faculty of Medicine, İstanbul, Turkey

Background: Anticoagulants are the mainstay of treatment for venous thromboembolism (VTE). Studies have shown conflicting results regarding statins ability to reduce the incidence of VTE.

Aims: To perform a network meta-analysis to determine which lipid-lowering agent was more efficacious in and had more evidence regarding reducing the VTE risk.

Study Design: Network meta-analysis of the randomized controlled trials (RCTs).

Methods: RCTs that assessed the effectiveness and safety of statins or fibrates and compared them to a placebo or another statin were eligible for the study. The outcomes examined in the study were deep vein thrombosis, pulmonary embolism, and/or VTE. We conducted a comprehensive search of the Medline database from 1966 to February 2017, using specific search terms related to VTE and statins. Additionally, we screened, and cross-checked relevant systematic reviews and meta-analyses. We performed a network meta-analysis to compare the different lipid-lowering agents to each other and the placebo and their effectiveness.

Results: Twenty-seven RCTs were included in the network meta-analysis (n = 137,940). Pairwise meta-analysis revealed a statistically significant lower incidence of VTE with statins than with placebos (0.79% vs 0.99%, respectively; risk ratios: 0.87, 0.77-0.98; $p = 0.022$). Rosuvastatin had the most favorable effect in reducing VTE risk than the other statins, fenofibrate, and placebo. Fenofibrate was ranked the worst drug choice, because it increased risk of VTE when compared with the other statins. Rosuvastatin was the best choice for reducing the VTE risk when compared with the placebo (OR: 0.56, 0.42-0.75), atorvastatin (OR: 0.64, 0.44-0.95), pravastatin (OR: 0.50, 0.34-0.74), simvastatin (OR: 0.60, 0.42-0.86) and fenofibrate (OR: 0.37, 0.25-0.56). Compared with a placebo, rosuvastatin reduced the VTE risk by around 45% and fenofibrate increased the risk by 65%.

Conclusion: Rosuvastatin is significantly reduces the risk of VTE when compared with a placebo, other statin subtypes, and fibrate. Furthermore, fenofibrate increased the VTE risk when compared with a placebo and statins.

Corresponding author: Oğuzhan Birdal, Atatürk University Faculty of Medicine, Department of Cardiology, Erzurum, Turkey
e-mail: droguzhanbirdal@gmail.com

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ORCID iDs of the authors: O.B. 0000-0002-0667-2516; M.S. 0000-0002-7258-2797; R.D. 0000-0003-3563-8779; O.T. 0000-0002-2774-8348; A.K. 0000-0002-0438-2021; İ.H.T. 0000-0003-4546-9227.

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INTRODUCTION

Venous thromboembolism (VTE), which encompasses pulmonary embolism and deep vein thrombosis (DVT), continues to pose a significant challenge in the field of healthcare. Although the medical agents used for the treatment of VTE are effective, bleeding issues remain an important concern for clinicians.[1] Studies have consistently demonstrated the efficacy of statins for both the primary and secondary prevention of cardiovascular diseases.[2,3] Statins have a favorable impact on inflammation and coagulation via the pleiotropic effect. In addition, they do not increase the risk of bleeding.[4,5] Venous and arterial thromboses frequently share common etiologic risk factors.[6] Therefore, this similarity prompted the hypothesis that statins could reduce the incidence of VTE beyond the favorable effect of reducing the LDL cholesterol level. Recent studies indicate that statin might reduce the incidence of VTE via the pleiotropic mechanism.[7-12] In one meta-analysis which included eight case-control and three cohort studies, Squizzato et al.[13] demonstrated that statins do not reduce the incidence of VTE. In contrast, two other meta-analyses conducted by Rahimi et al.[14] and Kunutsor et al.,[15] which incorporated multiple randomized controlled trials (RCTs), reached a consensus that statins significantly impacted and reduced the occurrence of VTE.

In this meta-analysis, we included both placebo-controlled and active-comparator RCTs to determine which lipid lowering agent, including statins, and fibrate, was more efficacious, and provided more evidence of reducing the VTE risk.

MATERIALS AND METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki and followed the guidelines outlined in the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions.[16]

Eligibility criteria

To be considered eligible, the study had to be an RCT assessing the effectiveness and safety of a statin or fibrate in comparison to a placebo or another statin. RCTs with a follow-up period of < 6 months were excluded. No restrictions were imposed on the medication dosage. Initially, all titles, and abstracts were screened to exclude studies that did not match the inclusion criteria. Subsequently, the full texts of the remaining articles were reviewed to identify eligible studies. RCTs that involved the concurrent use of niacin, ezetimibe, or antioxidant vitamins were excluded from the analysis. Furthermore, RCTs without reports published in the English language were also excluded.

Study outcomes

The study focused on evaluating the outcomes of DVT, PE, and/or VTE.

Study selection, data extraction, and assessment of the data quality

The Medline, EMBASE, and Cochrane databases were comprehensively and systematically searched from 1966 to February 2017. The following terms related to VTE were searched: "venous thromb*," "VTE," "deep vein thrombosis," and "pulmonary embolism." These terms were combined with search terms related to statins, including "statin," "HMG," "atorvastatin," "simvastatin," "statins," "lovastatin," "pravastatin," "fluvastatin," "fibrate," and "fenofibrate." The relevant systematic reviews and meta-analyses were meticulously screened and cross-checked. Two reviewers (I.H.T. and A.K) identified the eligible studies and extracted the key features from the included RCTs. The data quality was evaluated using the Cochrane Collaboration Risk of Bias Tool, which specifically assessed potential selection bias (randomization method and allocation concealment), information bias (blinding of outcome adjudicators), and analysis bias (intention-to-treat analysis and completeness of follow-up). Each study's overall risk of bias was categorized as low (all analyzed items were appropriate or at least five items were appropriate while the remaining two were unclear), unclear (more than two items were not reported), or high (at least one quality dimension indicated a possible bias).

Statistical Analysis

Two types of meta-analyses were conducted: pairwise and network. All statistical analyses were performed using STATA (version 14.0;).

For the pairwise meta-analysis, the summary risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) were calculated to evaluate the risk of VTE in lipid-lowering drugs and placebo. Both fixed-effects and random-effects models were utilized in the analysis. The random-effects model was employed when there was significant heterogeneity ($I^2 > 25\%$) among the outcomes. Conversely, in cases with low heterogeneity, the fixed-effects model was used. The level of heterogeneity was assessed using the I^2 statistic. Statistical significance was defined as a p value < 0.05 for two-tailed tests.

We conducted a network meta-analysis to compare the different lipid-lowering agents among themselves as well as with the placebo. Network meta-analysis enables the inclusion of both direct and indirect evidence, even if the treatments have not been directly compared in an RCT,[17-19] to obtain a more comprehensive and sensitive estimate.[20] The network meta-analysis was performed using the "mvmeta" command[21-23] and self-programmed routines in STATA (version 14.0;).[24] To evaluate the presence of small-study effects, a comparison-adjusted funnel plot was employed.

To identify inconsistencies within the network meta-analysis, a loop-specific approach was employed. This approach examines the consistency assumption within each closed loop of the network by comparing the direct and indirect estimates for a specific comparison, referred to as the inconsistency factor. The magnitude of the inconsistency factors and their corresponding 95% CIs were used to determine the presence of inconsistency in each loop. A common heterogeneity estimate within each loop was assumed. The analysis results were presented in a forest plot using the "ifplot" command in STATA (version 14.0;).

To facilitate the interpretation of heterogeneity results, the mean summary effects was presented alongside its predictive intervals

(PrIs). The PrI in the interval within which the estimate of a future study is expected to fall.

The ranking probabilities for all the treatments, indicating the likelihood of each intervention being at each possible rank, was calculated using the "mvmeta" command in STATA (version 14.0;).[22] Subsequently, a hierarchy of the competing interventions was derived using "rankograms".[25] To establish a treatment hierarchy, the surface under the cumulative ranking curve (SUCRA) and mean ranks was utilized. The relevant plots were generated using the Stata commands described by Chaimani et al.[24]

RESULTS

Study selection and patient population

We identified 299 potentially relevant studies through our electronic search. Among these, 55 studies were determined to be eligible. After further analyzing the 55 studies, 28 were excluded as they did not satisfy the inclusion criteria. Finally, a total of 27 RCTs were included in the network meta-analysis. The network structure of the lipid-lowering agents across these 27 RCTs is depicted in Figure 1. Efficacies of the placebo, fluvastatin, lovastatin, simvastatin, pravastatin, atorvastatin, rosuvastatin, and fenofibrate in included studies were evaluated. Overall, 137,940 patients were randomized to either study group. The demographic and clinical characteristics of the enrolled patients are shown in Table 1.

The risk of bias is shown in Figure 2. The quality of the RCT's was usually acceptable. The number of studies with a high risk of bias for random sequence generation and allocation concealment was low. However, there was a high risk of bias for blinding of participants and personnel in most of studies.

Network meta-analysis results

Conventional pairwise meta-analysis of the studies conducted with statins (23 RCT's) revealed a statistically significant lower incidence of VTE with statins than with placebos (incidence, 0.79% vs 0.99%, RR: 0.87, 0.77-0.98, $p = 0.022$). No significant heterogeneity was observed among the studies (I^2: 12.3%, $p = 0.293$). However, in the pooled analysis of the 23 RCTs with statins and one RCT with fenofibrate, the risk of VTE was comparable to that of RCTs with placebos. This may be attributable to the increased risk of VTE associated with fenofibrate (incidence, 0.91% vs 0.99%).

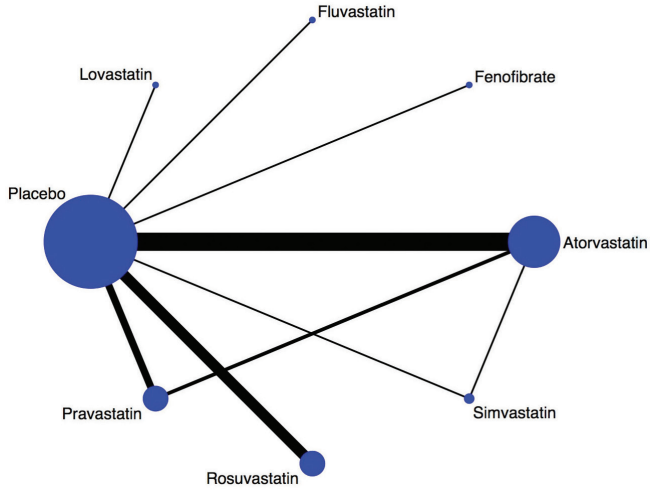

FIG. 1. Evidence network of the lipid-lowering agents.

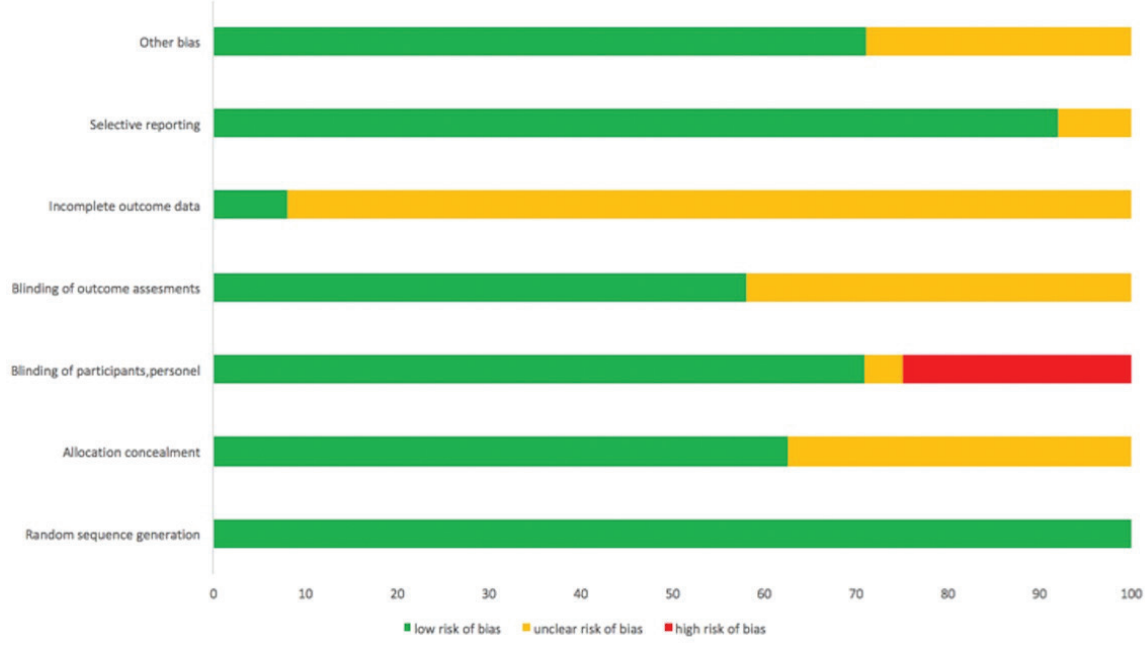

FIG. 2. Risk of bias.

TABLE 1. Summary of the Trial Characteristics.

Author, date	Name of the study	Patient population	Baseline year of the study	Age	Males (%)	Statin	Follow-up (years)
Sola, 2006	NR	Patients with non-ischemic HF and an LVEF ≤ 35	NR	≥ 18	33.0	Atorvastatin 20 mg	1.0
Nakamura, 2006	MEGA	Primary prevention	1994-1999	40-70	30.0	Pravastatin 10-20 mg	5.3
Kjekshus, 2007	CORONA	Patients with ischemic HF	NR	≥ 60	76.0	Rosuvastatin 10 mg	2.7
Crouse, 2007	METEOR	Primary prevention	2002-2006	45-70	57.0	Rosuvastatin 40 mg	2.0
GISSI-HF, 2008	GISSI-HF	Patients with CHF	2002-2005	≥ 18	77.0	Rosuvastatin 10 mg	3.9
Glynn, 2009	JUPİTER	Primary prevention	2003-2006	≥ 50	61.8	Rosuvastatin 20 mg	1.9
Feldman, 2010	LEADe	Patients with Alzheimer's disease	NR	50-90	48.0	Atorvastatin 80 mg	1.5
Chan, 2010	ASTRONOMER	Patients with mild-to-moderate aortic disease	2002-2005	18-82	61.0	Rosuvastatin 40 mg	3.5
Fasset, 2010	LORD	Patients with CKD	2002-2005	18-85	65.0	Atorvastatin 10 mg	2.5
Freeman, 2011	PROSPER	Elderly at increased vascular risk	1997-1999	70-82	47.0	Pravastatin 40 mg	3.2
Yusuf, 2016	HOPE-3 trial	Participants at intermediate cardiovascular risk	2007-2010	≥ 55	53.8	Rosuvastatin 10 mg	5.6
Downs, 1988	AFCAPS/ TexCAPS	Primary prevention	1990-1993	45-73	85.0	Lovastatin 20-40 mg	5.3
LIPID study group, 1998	LIPID	Patients with a history of MI or unstable angina	1990-1992	31-75	83.0	Pravastatin 40 mg	5.6
HPS study group, 2002	HPS	Patients with vascular disease or DM	1994-1997	40-80	75.0	Simvastatin 40 mg	5
Sever, 2003	ASCOTT-LLA	Patients with hypertension and other risk factors	1998-2000	40-79	81.0	Atorvastatin 10 mg	3.2
Fellstrom, 2004	ALERT	Renal transplant patients	NR	30-75	66.0	Fluvastatin 40 mg	5.1
Colhoun, 2004	CARDS	Patients with type 2 DM and other risk factors	1997-2001	40-75	68.0	Atorvastatin 10 mg	3.9
Asselbergs, 2004	PREVEND IT	Patients with microalbuminuria	1998-1999	28-75	65.0	Pravastatin 40 mg	3.8
Koren, 2004	ALLIANCE	Patients with CHD	1995-1998	> 18	82.0	Atorvastatin 10mg-80mg	4.3
Knopp, 2006	ASPEN	Patients with type 2 DM	1996-1999	40-75	66.0	Atorvastatin 10 mg	4.3
SPARCL investigators, 2006	SPARCL	Patients with stroke, TIA, or CHD	NR	NR	60.0	Atorvastatin 80 mg	4.9
Wanner, 2005	4D	Patients with diabetes and on hemodialysis	NR	18-80	54.0	Atorvastatin 20 mg	3.9
Cowell, 2005	SALTIRE	Patients with calcific aortic stenosis	2001-2002	> 18	70.0	Atorvastatin 80 mg	2.2
Smilde, 2001	ASAP	Patients with familial hypercholesterolaemia	1997-1998	30-70	40.0	Atorvastatin 80 mg vs Simvastatin 40 mg	2
Nissen, 2004	REVERSAL	Patients with CHD	1999-2001	30-75	72.0	Pravastatin 40 mg vs Atorvastatin 80 mg	1.5
Cannon, 2004	PROVE IT	Acute coronary syndrome	2000-2001	> 18	78.1	Pravastatin 40 mg vs Atorvastatin 80 mg	2.5
Keech, 2005	FIELD	Patients with type 2 DM	1998-2000	50-75	63.0	Fenofibrate	5

NR, Not reported; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; CORONA, Controlled Rosuvastatin in Multinational Trial in Heart Failure; METEOR, Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiac-Heart Failure; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LEADe, Lipitor's Effect in Alzheimer's Dementia; ASTRONOMER, Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin; LORD, Lipid Lowering, and Onset of Renal Disease; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk;HOPE-3, Heart Outcomes Prevention Evaluation (HOPE)-3 trial; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; LIPID, The Long-Term Intervention with Pravastatin in Ischemic Disease; HPS, Heart Protection Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; ALERT, Assessment of Lescol in Renal Transplant; CARDS, Collaborative Artovastatin Diabetes Study; PREVEND IT, Prevention of Renal, and Vascular Endstage Disease Intervention Trial; ALLIANCE, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASPEN, Artovastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TIA, transient ischemic attack; 4D, Die Deutsche Diabetes Dialyze; SALTIRE, Scottish Aortic Stenosis, and Lipid Lowering Trial, Impact on Regression; ASAP, Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia; REVERSAL, Reversal of Atherosclerosis with Aggressive Lipid Lowering; PROVE IT, Pravastatin, or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22; FIELD, Fenofibrate Intervention, and Event Lowering in Diabetes; HF, heart failure; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; CKD, chronic kidney disease; MI, myocardial infarction; DM, diabetes mellitus; CHD, coronary heart disease.

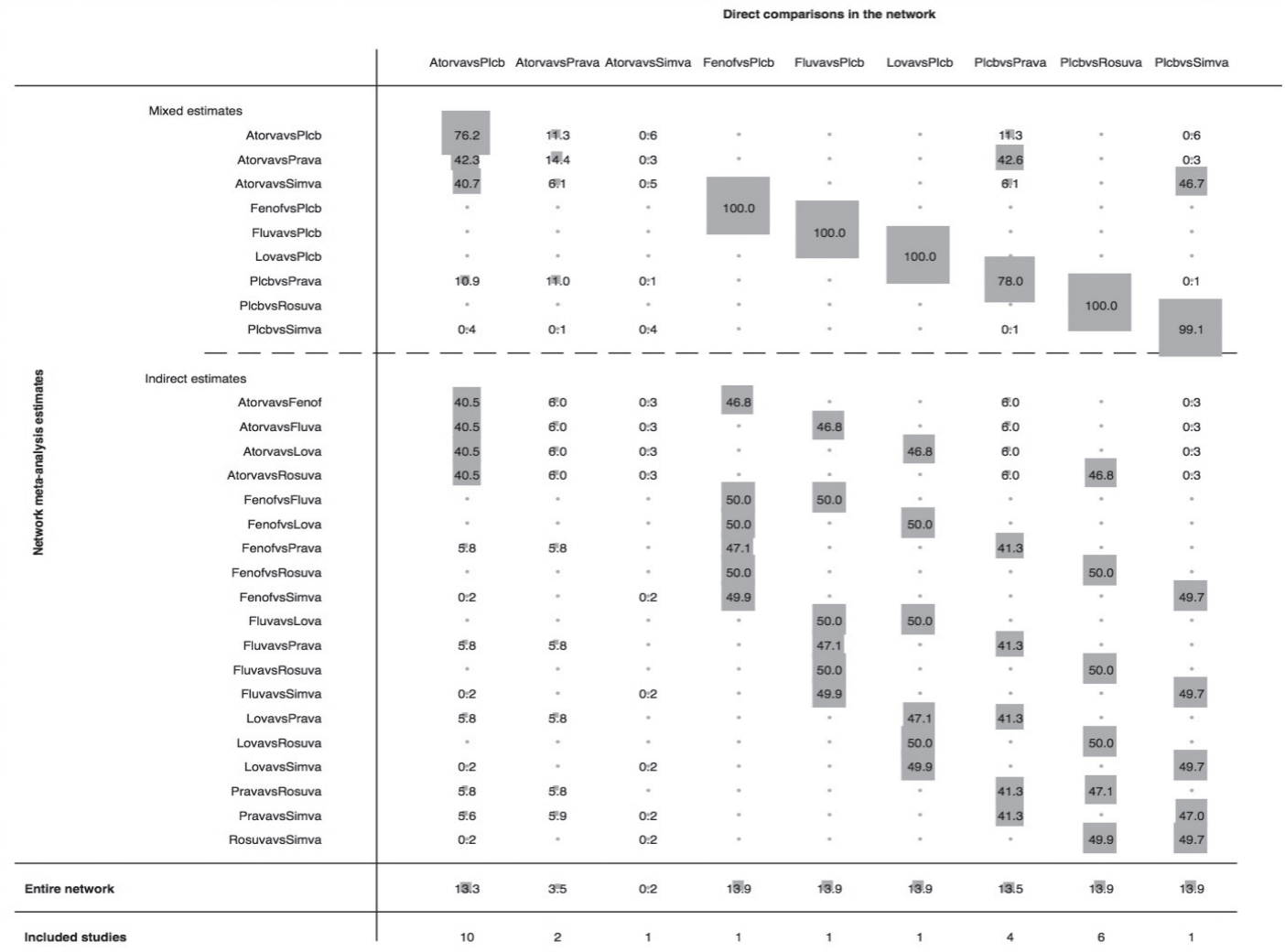

FIG. 3. Contribution plot of each direct comparison in the network. The figure depicts the percentage contribution of each direct comparison to the network summary estimates in the entire network.

Figure 3 illustrates of the contribution of each direct comparison to the estimation of the network summary effects. Among the total number of comparisons, nine were solely informed by direct evidence, nine were informed by a combination of direct and indirect evidence, and 19 were solely informed by indirect evidence. The contribution of the nine comparisons informed by direct evidence was well-balanced and comparable within the network. Furthermore, there was no inconsistency between the direct and indirect point estimates.

There were two closed loops identified in the network structure. All the CIs for the relative odds ratios (RoRs) were compatible with zero inconsistency, indicating that there was no significant deviation from consistency in the study outcomes (Figure 4). With an RoR value of one, there was no inconsistency between the direct and indirect evidence in the network.

Rosuvastatin had the most favorable effect on reducing the VTE risk among all statins, fenofibrate, and placebo. Fenofibrate was ranked

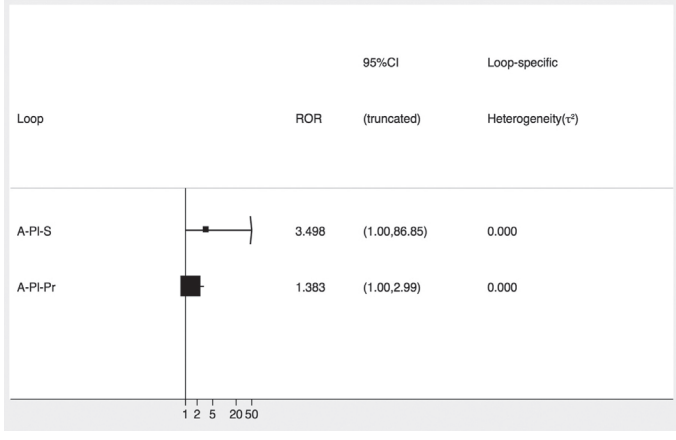

FIG. 4. Inconsistency plot for the risk of venous thromboembolism (VTE). The forest plot shows the ratio of the two odds ratios (RoR) from direct and indirect evidence in the loop. The confidence intervals are truncated at zero given that the direction of the inconsistency factor (IF) is unimportant.

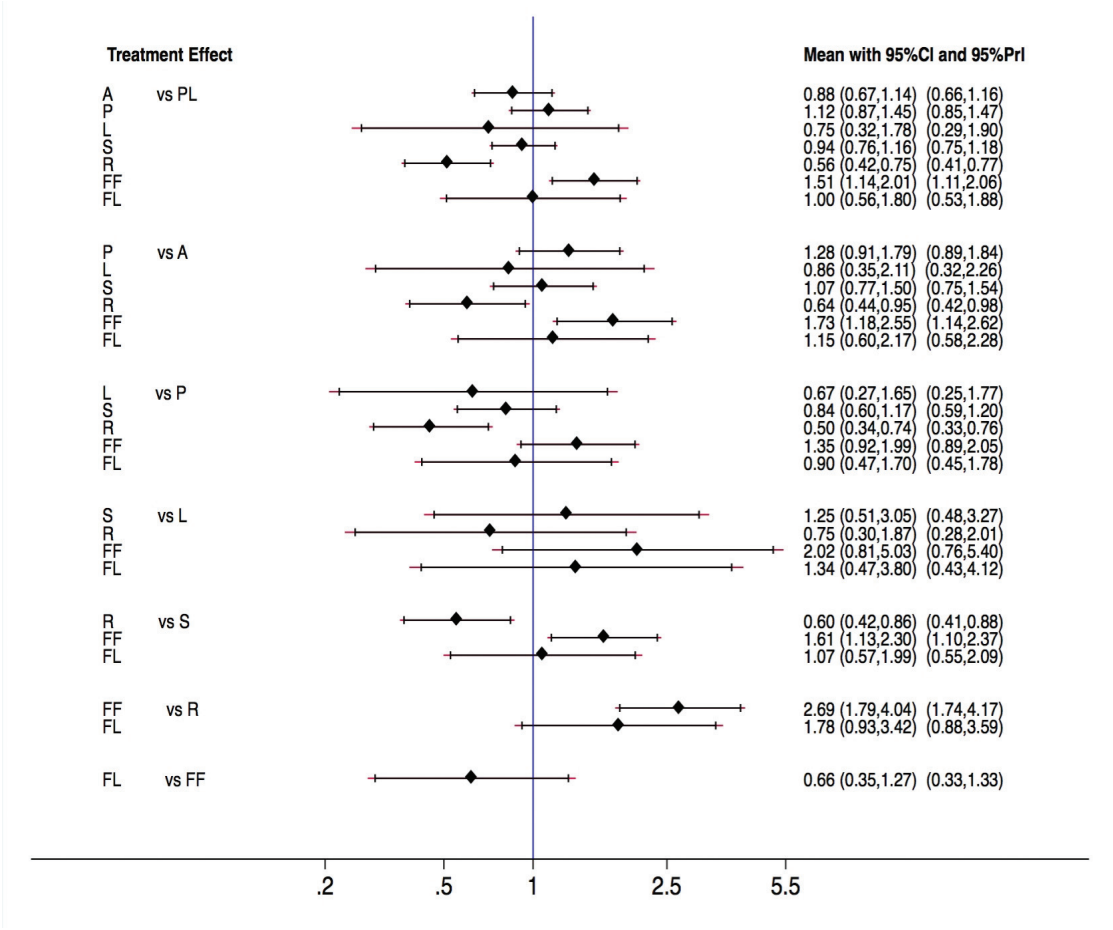

FIG. 5. Rankogram of the available lipid-lowering agents for reducing the risk of venous thromboembolism (VTE) based on the surface under the cumulative ranking curve (SUCRA).

the worst in terms of increased risk of VTE when compared with other statins. We ranked and compared the effects of all the drugs in relation to each other and the placebo, which were analyzed and evaluated using SUCRA probabilities (Figure 5). Rosuvastatin was ranked the highest for reducing VTE risk when compared with the placebo (OR: 0.56, 0.42-0.75), atorvastatin (OR: 0.64, 0.44-0.95), pravastatin (OR: 0.50, 0.34-0.74), simvastatin (OR: 0.60, 0.42-0.86), and fenofibrate (OR: 0.37, 0.25-0.56) (Figures 6 and 7). Compared with the placebo, rosuvastatin reduced the risk of VTE by around 45% and fenofibrate increased the risk of VTE by 65%. Figure 8 highlights the ranking of each lipid-lowering drugs for reducing the VTE risk. The probability of being the best drug to reduce VTE risk was > 50% (i.e., pure chance) for rosuvastatin (69.2%). The probability of being the worst drug that increased the VTE risk was > 50% for fenofibrate (80.6%). In our network analysis, the study size did not appear to influence the effect size. Additionally, the funnel plots for all the study outcomes exhibited symmetry around the zero line, indicating a lack of publication bias (Figure 9).

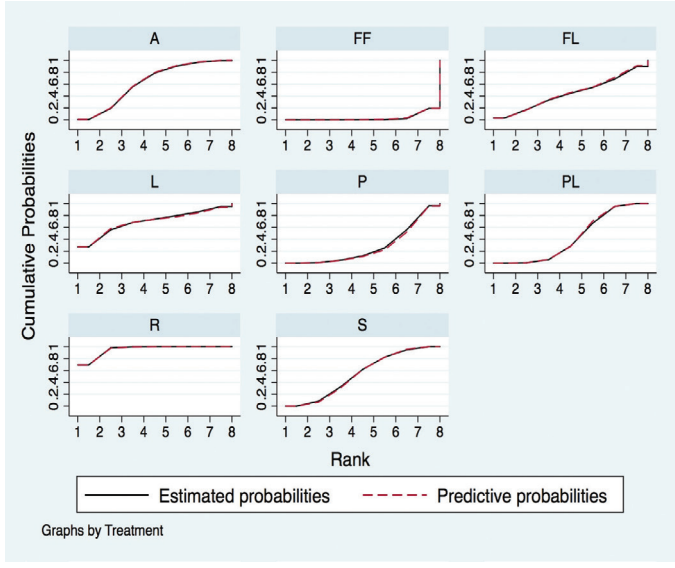

FIG. 6. Pooled odds ratio (95% confidence interval [CI]) determined by network meta-analysis for the risk of venous thromboembolism (VTE).

Placebo	0.88 (0.67,1.14)	1.12 (0.87,1.45)	0.75 (0.32,1.78)	0.94 (0.76,1.16)	0.56 (0.42,0.75)	1.51 (1.14,2.01)	1.00 (0.56,1.80)
1.14 (0.88,1.48)	Atorvastatin	1.28 (0.91,1.79)	0.86 (0.35,2.11)	1.07 (0.77,1.50)	0.64 (0.44,0.95)	1.73 (1.18,2.55)	1.15 (0.60,2.17)
0.89 (0.69,1.16)	0.78 (0.56,1.10)	Pravastatin	0.67 (0.27,1.65)	0.84 (0.60,1.17)	0.50 (0.34,0.74)	1.35 (0.92,1.99)	0.90 (0.47,1.70)
1.34 (0.56,3.17)	1.17 (0.47,2.89)	1.49 (0.61,3.69)	Lovastatin	1.25 (0.51,3.05)	0.75 (0.30,1.87)	2.02 (0.81,5.03)	1.34 (0.47,3.80)
1.07 (0.86,1.32)	0.93 (0.67,1.30)	1.19 (0.86,1.66)	0.80 (0.33,1.95)	Simvastatin	0.60 (0.42,0.86)	1.61 (1.13,2.30)	1.07 (0.57,1.99)
1.78 (1.33,2.37)	1.55 (1.05,2.29)	1.99 (1.35,2.93)	1.33 (0.53,3.31)	1.67 (1.16,2.38)	Rosuvastatin	2.69 (1.79,4.04)	1.78 (0.93,3.42)
0.66 (0.50,0.88)	0.58 (0.39,0.85)	0.74 (0.50,1.08)	0.49 (0.20,1.23)	0.62 (0.43,0.88)	0.37 (0.25,0.56)	fenofibrate	0.66 (0.35,1.27)
1.00 (0.56,1.79)	0.87 (0.46,1.66)	1.12 (0.59,2.11)	0.75 (0.26,2.12)	0.94 (0.50,1.74)	0.56 (0.29,1.08)	1.51 (0.79,2.90)	Fluvastatin

FIG. 7. League table for the risk of venous thromboembolism (VTE).

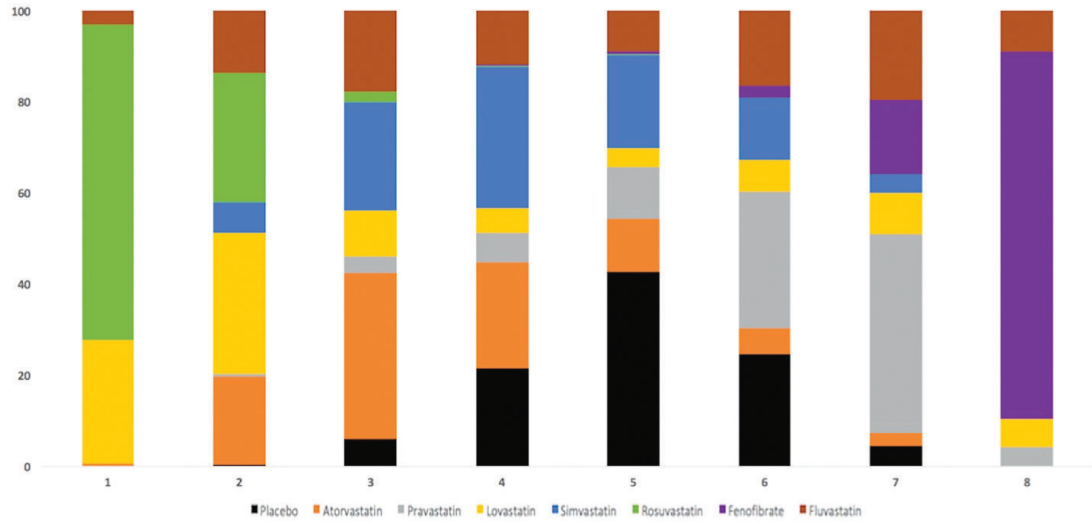

FIG. 8. Ranking of the treatment strategies regarding the risk of venous thromboembolism (VTE). Bar plots have been utilized for ranking the probabilities of each treatment strategy. The possible rank of each strategy is represented on the x-axis (from best to worst) and the probability of each strategy to be at a specific rank is on the y-axis.

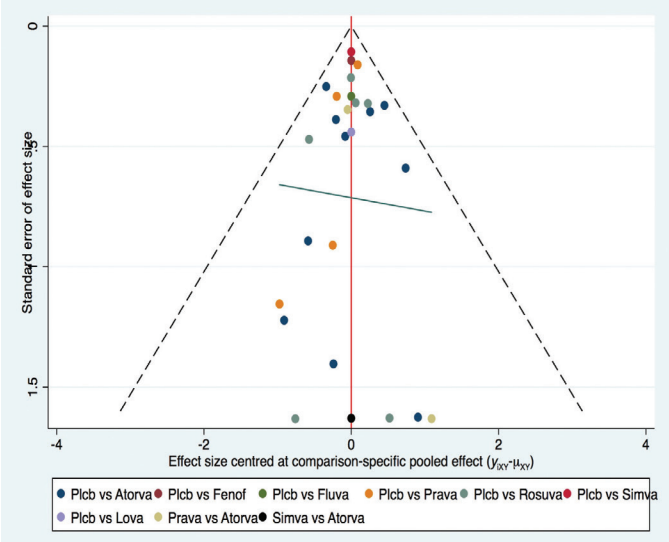

FIG. 9. Comparison-adjusted funnel plot for the risk of venous thromboembolism (VTE). The red line represents a null hypothesis, indicating that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The two black dashed lines represent a 95% CI for the difference between study-specific sizes and comparison-specific summary estimates. Y_{iXY} is the noted effect size in study I that compares x with y. μ_{XY} is the comparison-specific summary estimate for x versus y.

DISCUSSION

Despite the comprehensive evidence of long-term efficacy and safety of lipid-lowering agents, including pairwise, and network meta-analyses, data related to their impact on VTE are sparse. Our report is the first meta-analysis conducted on the impact of lipid-lowering agent on VTE risk that included 28 RCTs and a total of 137,000 patients. Our analysis revealed that rosuvastatin is significantly associated with a reduced risk of VTE compared with placebo, other statin subtypes, and fibrate. Fenofibrate showed an increased risk of VTE when compared with both the placebo and statins. These findings highlight the differential effects of various lipid-lowering agents on the risk of VTE. The other statin subgroups, aside from rosuvastatin, demonstrated similar effects on the risk of VTE when compared with the placebo. Thus, the overall impact of statins, excluding rosuvastatin, on the VTE risk did not significantly differ from that of placebos.

Our pairwise meta-analysis demonstrated that compared with the placebo, statins reduced the risk of VTE when the analysis was confined to only studies involving statins (23 RCT's) (incidences, 0.79% vs 0.99%; RR: 0.87, 0.77-0.98, p = 0.022). However, in the pooled analysis of 23 statin-related RCTs and one fenofibrate-related RCT, the risk of VTE was similar to that with placebo, predominantly due to the increased risk with fenofibrate use

(incidences, 0.91% vs 0.99%). These findings are comparable to those of previous meta-analyses, further strengthening the consistency of the evidence across studies.[13,15,26] Our network meta-analysis demonstrated that rosuvastatin had the lowest VTE risk than the other statin substypes and fenofibrate did. Fenofibrate ranked the worst drug choice because it increased the risk of VTE. Rosuvastatin was ranked the best drug choice for reducing VTE risk when compared with the placebo (OR: 0.56, 0.42-0.75), atorvastatin (OR: 0.64, 0.44-0.95), pravastatin (OR: 0.50, 0.34-0.74), simvastatin (OR: 0.60, 0.42-0.86) and fenofibrate (OR: 0.37, 0.25-0.56). Furthermore, the probability of being the best drug to reduce VTE was > 50% for rosuvastatin (69.2%), and the probability of being the worst drug was > 50% for fenofibrate (80.6%). These findings indicate that the reduced risk of VTE with statins is mainly associated with rosuvastatin.

In a meta-analysis that included an RCT and nine observational studies, Agarwal et al.[26] demonstrated that statins were associated with a reduced risk of VTE. This result was similar to that of the study by Kunutsor et al.[15] Rosuvastatin appears to have a beneficial effect on VTE events when compared with other statins. Our network meta-analysis that demonstrated that statins reduced the risk of VTE, included the aforementioned studies. However, we also found a significant difference between the effects of different statin groups on VTE risk. Only rosuvastatin was significantly associated with a reduced risk of VTE when compared with placebo; the other statin subgroups had a similar effect to that of placebos. The risk of VTE was significantly higher with fenofibrate administration that with statins and placebos.

Statins have a strong vasculo-protective effect in addition to being lipid-lowering agents. The anti-inflammatory and anti-thrombotic properties of statins are considered to be responsible for the vasculo-protective effect; this leads to the alteration of endothelial dysfunction and blood flow, which opposes the hypercoagulable states. The pairwise meta-analyses results showing that statins reduced the VTE risk can be partly explained by these mechanisms. However, in our network meta-analysis, rosuvastatin alone was associated with a reduced risk of VTE. This can be partly attributed to the inherent properties of rosuvastatin, including its more potent lipid-lowering and anti-inflammatory effects, which produces a more pronounced decrease in CRP level and prominent vascular protection (anti-atherogenic).[27-30]

Fibrates are peroxisome proliferator-activated receptor activators that reduce the procoagulant activity and enhance fibrinolysis.[31-33] Although, fibrates are generally thought to have anti-thrombotic activities, in our network meta-analysis, they were associated with an increased risk of VTE when compared with both statins and the placebo. This can be attributed to the increased homocysteine levels associated with fibrates; however, this remains debatable.[34]

Ongoing studies and reviews almost always show a relationship between anti-coagulation and statin therapies. However, the mechanism by which statins cause anti-coagulant or protective effects against VTE remains a debate. Although there are theories regarding the mechanism of these effects, there is no hard evidence.[35,36]

RCT results indicate a potential beneficial effect of rosuvastatin in the prevention of VTE, while suggesting a harmful effect of fibrate use in relation to VTE. However, further studies are necessary to validate these hypotheses and draw definitive conclusions. While our analysis provides valuable insights, additional studies, and robust evidence are required to confirm the observed associations and establish conclusive findings.

VTE is a frequently encountered in clinical practice and has substantial implications in terms of morbidity and mortality. The potential utilization of rosuvastatin for the prevention of VTE could present an additional indication for this medication. This could expand the therapeutic applications of rosuvastatin and potentially improve patient outcomes by reducing the risk of VTE. However, further research and clinical trials are warranted to establish the efficacy and safety of rosuvastatin for VTE prevention, before it can be used worldwide or any definitive recommendations can be made.

The present meta-analysis has several limitations. An important limitation is the variability in the study population characteristics, which is inherent to any meta-analysis. This heterogeneity in participant characteristics may have introduced a potential bias and limited the generalizability of the study findings.

The COVID-19 pandemic caused a new wave of VTE cases.[37] Most of the studies included were conducted before the pandemic. Inclusion of studies conducted after the pandemic may change the outcomes of our analyses.

Another limitation of the study is the variation in statin dosages used. The different dosages may have influenced the effectiveness and safety outcomes and could potentially impact the overall results of the network meta-analysis.

Most of the trial evidence used in this study was based on previously unpublished data, which were only recently made available through two reviews. This reliance on unpublished data may have introduced a publication bias and limited the comprehensiveness of the analysis.

Due to the limited number of studies available for the outcomes of DVT and PE, further analysis of these data was not possible. This limitation highlights the need for more studies in these specific areas.

Finally, the trial evidence mainly relied on previously unpublished data, which were collected as adverse events and contributed by investigators. This may introduce have introduced potential biases in the estimates of the analyses.

Considering these limitations, our network meta-analyses findings should be interpreted with caution. Furthermore, there is a need for additional high-quality studies with larger sample sizes and standardized statin dosages to further investigate the effectiveness and safety of statins in relation to VTE.

The present network meta-analysis revealed that rosuvastatin was significantly associated with a reduced risk of VTE, while fenofibrate was associated with an increased VTE risk. Except for

rosuvastatin, all other statin subgroups had a neutral effect on the risk of VTE.

Ethics Committee Approval: Since our article was a meta-analysis, we did not receive ethics committee approval.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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