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

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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 a 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.
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. Studies have consistently demonstrated the efficacy of statins for both the primary and secondary prevention of cardiovascular diseases. Statins have a favorable impact on inflammation and coagulation via the pleiotropic effect. In addition, they do not increase the risk of bleeding. Venous and arterial thromboses frequently share common etiologic risk factors. 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. In one meta-analysis which included eight case-control and three cohort studies, Squizzato et al. demonstrated that statins do not reduce the incidence of VTE. In contrast, two other meta-analyses conducted by Rahimi et al. and Kunutsor et al., 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.

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 (I² > 25%) among the outcomes. Conversely, in cases with low heterogeneity, the fixed-effects model was used. The level of heterogeneity was assessed using the I² 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. To obtain a more comprehensive and sensitive estimate. The network meta-analysis was performed using the “mvmeta” command and self-programmed routines in STATA (version 14.0). 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). Subsequently, a hierarchy of the competing interventions was derived using “rankograms”. 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.

**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 binding 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 (I²: 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.](image1)

![FIG. 2. Risk of bias.](image2)
<table>
<thead>
<tr>
<th>Author, date</th>
<th>Name of the study</th>
<th>Patient population</th>
<th>Baseline year of the study</th>
<th>Age</th>
<th>Males (%)</th>
<th>Statin follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sola, 2006</td>
<td>NR</td>
<td>Patients with non-ischemic HF and an LVEF ≤ 35</td>
<td>NR</td>
<td>≥ 18</td>
<td>33.0</td>
<td>Atorvastatin 20 mg</td>
</tr>
<tr>
<td>Nakamura, 2006</td>
<td>MEGA</td>
<td>Primary prevention</td>
<td>1994-1999</td>
<td>40-70</td>
<td>30.0</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td>Kjekshus, 2007</td>
<td>CORONA</td>
<td>Patients with ischemic HF</td>
<td>NR</td>
<td>≥ 60</td>
<td>76.0</td>
<td>Rosuvastatin 10 mg</td>
</tr>
<tr>
<td>Crouse, 2007</td>
<td>METEOR</td>
<td>Primary prevention</td>
<td>2002-2006</td>
<td>45-70</td>
<td>57.0</td>
<td>Rosuvastatin 40 mg</td>
</tr>
<tr>
<td>GISSI-HF, 2008</td>
<td>GISSI-HF</td>
<td>Patients with CHF</td>
<td>2002-2005</td>
<td>≥ 18</td>
<td>77.0</td>
<td>Rosuvastatin 10 mg</td>
</tr>
<tr>
<td>Glynn, 2009</td>
<td>JUPITER</td>
<td>Primary prevention</td>
<td>2003-2006</td>
<td>≥ 50</td>
<td>61.8</td>
<td>Rosuvastatin 20 mg</td>
</tr>
<tr>
<td>Feldman, 2010</td>
<td>LEADe</td>
<td>Patients with Alzheimer’s disease</td>
<td>NR</td>
<td>50-90</td>
<td>48.0</td>
<td>Atorvastatin 80 mg</td>
</tr>
<tr>
<td>Chan, 2010</td>
<td>ASTRONOMER</td>
<td>Patients with mild-to-moderate aortic disease</td>
<td>2002-2005</td>
<td>18-82</td>
<td>61.0</td>
<td>Rosuvastatin 40 mg</td>
</tr>
<tr>
<td>Fasset, 2010</td>
<td>LORD</td>
<td>Patients with CKD</td>
<td>2002-2005</td>
<td>18-85</td>
<td>65.0</td>
<td>Atorvastatin 10 mg</td>
</tr>
<tr>
<td>Freeman, 2011</td>
<td>PROSPER</td>
<td>Elderly at increased vascular risk</td>
<td>1997-1999</td>
<td>70-82</td>
<td>47.0</td>
<td>Pravastatin 40 mg</td>
</tr>
<tr>
<td>Yusuf, 2016</td>
<td>HOPE-3 trial</td>
<td>Participants at intermediate cardiovascular risk</td>
<td>2007-2010</td>
<td>≥ 55</td>
<td>53.8</td>
<td>Rosuvastatin 10 mg</td>
</tr>
<tr>
<td>Downs, 1988</td>
<td>LIPID study group, 1998</td>
<td>Patients with a history of MI or unstable angina</td>
<td>1990-1992</td>
<td>31-75</td>
<td>83.0</td>
<td>Pravastatin 40 mg</td>
</tr>
<tr>
<td>HPS study group, 2002</td>
<td>HPS</td>
<td>Patients with vascular disease or DM</td>
<td>1994-1997</td>
<td>40-80</td>
<td>75.0</td>
<td>Simvastatin 40 mg</td>
</tr>
<tr>
<td>Sever, 2003</td>
<td>ASCOTT-LLA</td>
<td>Patients with hypertension and other risk factors</td>
<td>1998-2000</td>
<td>40-79</td>
<td>81.0</td>
<td>Atorvastatin 10 mg</td>
</tr>
<tr>
<td>Fellstrom, 2004</td>
<td>ALERT</td>
<td>Renal transplant patients</td>
<td>NR</td>
<td>30-75</td>
<td>66.0</td>
<td>Fluvastatin 40 mg</td>
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<tr>
<td>Colhoun, 2004</td>
<td>CARDS</td>
<td>Patients with type 2 DM and other risk factors</td>
<td>1997-2001</td>
<td>40-75</td>
<td>68.0</td>
<td>Atorvastatin 10 mg</td>
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<tr>
<td>Axelbergs, 2004</td>
<td>PREVEND IT</td>
<td>Patients with microalbuminuria</td>
<td>1998-1999</td>
<td>28-75</td>
<td>65.0</td>
<td>Pravastatin 40 mg</td>
</tr>
<tr>
<td>Koren, 2004</td>
<td>ALLIANCE</td>
<td>Patients with CHD</td>
<td>1995-1998</td>
<td>&gt; 18</td>
<td>82.0</td>
<td>Atorvastatin 10mg-80mg</td>
</tr>
<tr>
<td>Knopp, 2006</td>
<td>ASPEN</td>
<td>Patients with type 2 DM</td>
<td>1996-1999</td>
<td>40-75</td>
<td>66.0</td>
<td>Atorvastatin 10 mg</td>
</tr>
<tr>
<td>SPARCL investigators, 2006</td>
<td>SPARCL</td>
<td>Patients with stroke, TIA, or CHD</td>
<td>NR</td>
<td>NR</td>
<td>60.0</td>
<td>Atorvastatin 80 mg</td>
</tr>
<tr>
<td>Wanner, 2005</td>
<td>4D</td>
<td>Patients with diabetes and on hemodialysis</td>
<td>NR</td>
<td>18-80</td>
<td>54.0</td>
<td>Atorvastatin 20 mg</td>
</tr>
<tr>
<td>Cowell, 2005</td>
<td>SALTIRE</td>
<td>Patients with calcific aortic stenosis</td>
<td>2001-2002</td>
<td>&gt; 18</td>
<td>70.0</td>
<td>Atorvastatin 80 mg</td>
</tr>
<tr>
<td>Smilde, 2001</td>
<td>ASAP</td>
<td>Patients with familial hypercholesterolaemia</td>
<td>1997-1998</td>
<td>30-70</td>
<td>40.0</td>
<td>Atorvastatin 80 mg vs Simvastatin 40 mg</td>
</tr>
<tr>
<td>Nissen, 2004</td>
<td>REVERSAL</td>
<td>Patients with CHD</td>
<td>1999-2001</td>
<td>30-75</td>
<td>72.0</td>
<td>Pravastatin 40 mg vs Atorvastatin 80 mg</td>
</tr>
<tr>
<td>Cannon, 2004</td>
<td>PROVE IT</td>
<td>Acute coronary syndrome</td>
<td>2000-2001</td>
<td>&gt; 18</td>
<td>78.1</td>
<td>Pravastatin 40 mg vs Atorvastatin 80 mg</td>
</tr>
<tr>
<td>Keech, 2005</td>
<td>FIELD</td>
<td>Patients with type 2 DM</td>
<td>1998-2000</td>
<td>50-75</td>
<td>63.0</td>
<td>Fenofibrate</td>
</tr>
</tbody>
</table>

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’Insufficienza cardiaca-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; REVERSAL, Assessment of Lescol in Renal Transplant; CARDS, Collaborative Arterosclerosis Prevention Study; PREVEND IT, Prevention of Renal, and Vascular Endstage Disease Intervention Trial; ALLE, Assessement of Lescol in Renal Transplant; CARDS, Collaborative Arterosclerosis Prevention Study; PROVIT2, Prevention of Renal, and Vascular Endstage Disease Intervention Trial; ALLIANCE, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASPEN, Arterosclerosis Prevention 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 Dialyse; 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.
Figure 3 illustrates 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 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. 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).

FIG. 6. Pooled odds ratio (95% confidence interval [CI]) determined by network meta-analysis for the risk of venous thromboembolism (VTE).
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 agents 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 and statins. 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.
levels associated with fibrates; however, this remains debatable. The placebo. This can be attributed to the increased homocysteine and an increased risk of VTE when compared with both statins and lipid-lowering agents. The anti-inflammatory and anti-thrombotic protection (anti-atherogenic).

Fibrates are peroxisome proliferator-activated receptor activators (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. Our network meta-analysis demonstrated that rosuvastatin had the lowest VTE risk than the other statin subtypes 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. demonstrated that statins were associated with a reduced risk of VTE. This result was similar to that of the study by Kunutsor et al. 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 placebo. The risk of VTE was significantly higher with fenofibrate administration than 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 opposers 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).

Fibrates are peroxisome proliferator-activated receptor activators that reduce the procoagulant activity and enhance fibrinolysis. 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.

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.

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.

Study limitations

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. 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 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 rosvastatin, 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.

**Author Contributions:** Concept- O.B.; Design- O.B., A.K., İ.H.T.; Data Collection or Processing- M.S., R.D.; Analysis or Interpretation- A.K.; Literature Search- R.D.; Writing- O.B., O.T.

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