CLINICAL RESEARCH

Statins, fibrates, and venous thromboembolism: a meta-analysis

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Aims	The aim is to make a systematic review of the literature to assess the effect of lipid-lowering drugs on venous thromboembolism (VTE) occurrence.
Methods and results	MEDLINE and EMBASE databases were searched to identify studies that evaluated the effect of lipid-lowering drugs, in particular statins and fibrates, on VTE risk until April 2009. A scoring system was used to divide studies into two quality categories. Odds ratios (ORs) and 95% confidence intervals (CIs) were then calculated and pooled using a fixed and a random-effects model. Statistical heterogeneity was evaluated through the use of I^2 statistics. Three randomized controlled trials (RCTs), three cohort, and eight case−control studies were included in our systematic review, for a total of 863 805 patients. Statins use significantly reduced VTE risk [OR, 0.81; 95% CI, 0.66−0.99, random-effect model)]. There was a very high heterogeneity among the studies ($I^2 > 80\%$). The use of fibrates was associated with a significant increase in the risk of VTE (OR, 1.58; 95% CI, 1.23−2.02), without heterogeneity ($I^2 = 0\%$). Data on other lipid-lowering drugs were lacking.
Conclusion	This meta-analysis of available literature suggests that statins may lower the risk of VTE, whereas fibrates may increase this risk. Due to several methodological limitations, this conclusion should be considered with caution, and additional, specifically designed RCTs are warranted.
Keywords	Statins • Fibrates • Venous thromboembolism

Introduction

Lipid-lowering drugs are a wide group of molecules including the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), fibrates, cholesterol absorption inhibitors, bile acid sequestrants, niacin, and fish oil. They are widely used in the management of patients with hyperlipidaemia and in the primary and secondary prevention of atherosclerotic disease.[1] Several biochemical effects have been advocated in addition to modifying lipid profile.[2] Among them, interactions with the haemostatic system and with antithrombotic drugs have been described, but the clinical relevance of these properties is still unclear.[3] Observational studies have reported a reduced risk for venous thromboembolism (VTE), i.e. deep venous thrombosis (DVT) and pulmonary embolism (PE), in patients on statins treatment and an increased risk for VTE in patients on fibrates treatment.[4] Although this effect, if true, may be associated with a modified lipid profile, the hypothesis of a clinically relevant role of lipid-lowering drugs on the coagulation system remains intriguing.[5]

The primary aim of our systematic review was to assess the effect of lipid-lowering drugs, in particular statins and fibrates, on the risk of VTE.

Methods

Study identification

We attempted to identify all published studies that evaluated the effects of lipid-lowering drugs on VTE risk using the MEDLINE (1966 to April Week 1 2009) and EMBASE (1980 to April Week 2 2009) electronic databases. The following search terms (textwords and MeSH or EMTREE terms, respectively) were used for the MEDLINE search: Hydroxymethylglutaryl-CoA Reductase Inhibitors, Anticholesteremic Agents, Clofibric Acid, Antilipemic Agents, Statins, Fibrates, Embolism

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and Thrombosis, Venous Thromboembolism, Vein Thrombosis; and for the EMBASE database search: Hydroxymethylglutaryl Coenzyme A Reductase Inhibitor, Ezetimibe, Fibric Acid, Antilipemic Agent, Omega 3 Fatty Acid, Vein thrombosis, Venous Thromboembolism.

The search strategy was developed without any language restriction. Reference lists of all studies included in the present systematic review were screened for potential additional eligible studies. A letter and/or e-mail were sent to the corresponding author if the full manuscript was unavailable.

Study selection

Two authors (M.G., E.R.) independently reviewed all selected titles and abstracts. Studies were excluded if the title and/or abstract was not appropriate for the aim of our review. Full texts were subsequently obtained for eligible studies or when the relevance of an article could not be excluded with certainty. Disagreement was resolved by consensus and by opinion of a third reviewer (A.S.), if necessary. Selected studies were eligible if they met the following criteria: patients were 18 years or older and at least 100 patients were enrolled. Both observational and experimental studies were included. Reviews, case-reports, and non-human studies were excluded.

Data extraction and quality assessment

For randomized controlled trials (RCTs), we planned quality assessment by means of Jadad's scale, which evaluates the following three study characteristics: method of randomization, method of blinding, and follow-up.[6] To stratify RCTs, we applied the following cut-offs: a total of five points defined high quality studies; three and four points defined medium quality studies; two or less points defined low quality studies.

Although in observational studies the use of quality scoring systems or quality scales is controversial,[7] study quality was assessed by the following items for cohort studies: type of study (prospective or retrospective); patient selection (consecutive patients without potential bias of selection); control group (consecutive enrolment or matched for age and sex). For each fulfilled item one point was given. A scoring system was adapted to identify three quality categories as follows: a total of three points defined high quality studies; two or less point defined low quality studies. The total number of patients lost to follow-up (less than 5% of patients, more than 20%, or between 5 and 20%) was also ascertained as an additional quality item. For case−control studies, the following items assessed study quality: patient selection (consecutive patients without potential bias of selection); control group (consecutive enrolment or matched for age and sex). A total of two points defined high-quality studies; one or less defined a low-quality study. The total number of cases was also ascertained as an additional quality item.

One reviewer (M.G.) completed the data extraction form. A second reviewer (A.S.) checked the extracted data. The following characteristics were collected: (i) total number of enrolled patients; (ii) follow-up duration for RCTs and cohort studies; (iii) VTE diagnosis (objective or clinical); (iv) inclusion or exclusion or patients with previous VTE; (v) type of lipid-lowering drugs; (vi) molecule and dosage; (vii) use of lipid-lowering drugs for primary or secondary prevention of cardiovascular diastase; (viii) outcomes: for RCTs and cohort studies these included total VTE events, DVT, and PE; for case−control studies, the use of any lipid-lowering drugs. In case data were available for both current and past lipid-lowering drug use, we included in the meta-analysis only current use. Corresponding author was contacted for additional data in case absolute values were not provided in the manuscript.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. These data were pooled using a fixed-effects model (the Mantel−Haenszel method),[8] and comparing these findings with the results obtained using a random-effects model (the DerSimionan and Laird method), in particular in case of significant statistical heterogeneity.[9] In case of high statistical heterogeneity, results using random-effects model are reported. Statistical heterogeneity was evaluated using the I^2 statistic, which assesses the appropriateness of pooling the individual study results.[10] The I^2 value provides an estimate of the amount of variance across studies due to heterogeneity rather than chance. $I^2 < 30\%$ indicates mild heterogeneity, 30−50% moderate, and $>50\%$ severe heterogeneity. When heterogeneity was present, we repeated the analysis removing one study at time to assess the source of heterogeneity.

Presence of publication bias was explored using funnel plots of effect size against standard error.[11]

The software Review Manager (RevMan, version 5.0.16 for Windows, Oxford, UK; The Cochrane Collaboration, 2008) supported the analysis.

Results

Study identification and selection

We identified 1552 potentially relevant studies from the following databases: 977 from EMBASE and 575 from MEDLINE. We excluded 1526 studies after title and abstract screening using predefined inclusion and exclusion criteria; the remaining 26 studies were retrieved in full for detailed evaluation. Three additional studies were identified through manual review of references. Of the 29 retrieved studies, 15 were excluded for the following reasons: 8 did not match inclusion criteria, 5 were editorial or narrative review, and 2 reported duplicated data.[12,13] Fourteen studies were therefore included in this systematic review.[14−27] The study identification and selection progression is summarized in Figure 1.

Study characteristics

Baseline characteristics of patients included in the studies were summarized in Table 1. All studies were written in English. Studies ranged in size from 228[23] to 614 000 patients,[19] for a total of 863 805 included patients. Three RCTs,[14−16] three cohort,[17−19] and eight case−control studies[20−27] were included in our systematic review. Twelve studies, i.e. one RCT, three cohort, and eight case−control studies, including 850 118 patients assessed the effect of statins on the risk of VTE.[16−27] Three studies, i.e. two RCTs and one case−control study, including a total 15 041 patients assessed the effect of fibrates on the risk of VTE.[14,15,22] One of these two RCTs including 5010 patients also assessed the effect of niacin on the risk of VTE.[14] Five studies including 61 971 patients assessed, in addition to the effect of statins, the effect of lipid-lowering drugs other than statins on VTE risk without specifying which drug was used.[17,20,21,25,26] We found no studies that have assessed the effect of cholesterol absorption inhibitors, bile acid sequestrants, or fish oil on the risk of VTE.

Figure 1 Studies' selection progression.
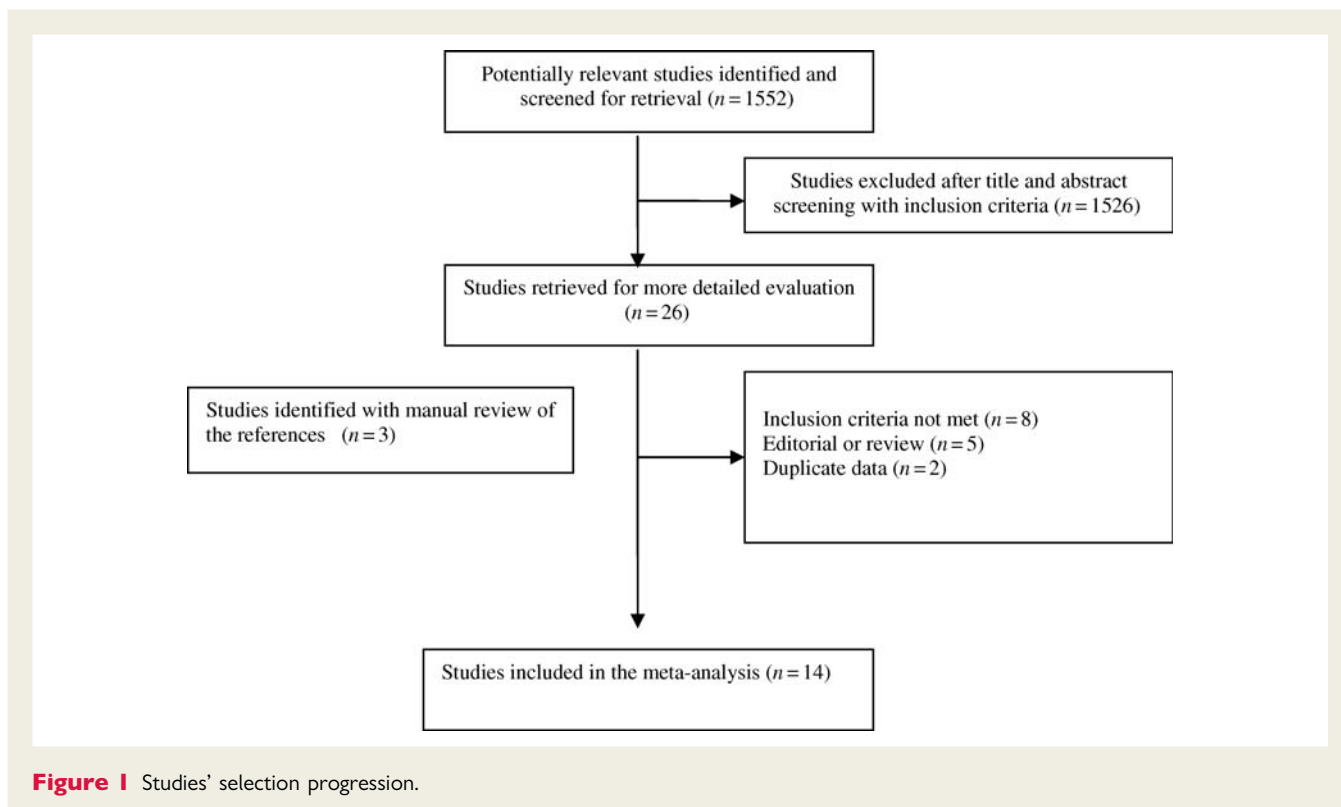
Study quality

Quality assessment items are summarized in *Table 2*. Two of the three RCTs were of high quality, but the incidence of VTE was not a primary endpoint in any of these studies.[15,16] All three cohort studies were of low quality. Four (50%) case–control studies were of high quality.[22,24,26,27]

Statins

The use of statins was found to significantly decrease the risk of VTE at random-effects model analysis (OR, 0.81; 95% CI, 0.66–0.99, *Figure 2*). There was a very high heterogeneity among the studies ($I^2 > 80\%$, $P < 0.05$), which was caused by the case–control and cohort studies. Removing one study at time, no significant modification of overall heterogeneity was identified. Among cohort studies, the study by Smeeth *et al.*[19] mainly contributed to statistical heterogeneity. After exploring results and heterogeneity according to study designs, no significant differences were noted in ORs and in I^2 between cohort and case–control studies (*Figure 2*). Funnel plot is shown in *Figure 3*, and shows no indication of publication bias.

When we pooled data from the five high-quality studies, the OR remained similar (OR, 0.75; 95% CI, 0.54–1.04, random-effects model) with a persistent high heterogeneity ($I^2 > 80\%$).[16,22,24,26,27] Only two studies provided adequate data on the risk of PE alone[16,24] and only three studies provided adequate data on the risk of DVT alone.[16,17,24] No significant differences were detected when these studies were separately analysed (at random-effects model: OR, 1.12; 95% CI, 0.63–1.99 for PE and OR, 0.72; 95% CI, 0.50–1.03 for DVT). Two studies provided data on unprovoked VTE events: at random-effects model, the

OR was 0.83 (95% CI, 0.56–1.25).[16,27] A sensitivity analysis on potential differences among statins and on potential dose-dependent effects could not be performed, because adequate data on pravastatin, rosuvastatin, and simvastatin were available in only two, one, and one studies, respectively[16,21,23].

Fibrates

The use of fibrates was found to increase the risk of VTE (OR, 1.66; 95% CI, 1.35–2.04, fixed-effects model, *Figure 4*). There was no heterogeneity among the studies ($I^2 = 0\%$). The analysis was repeated using random-effects model and yielded similar results (OR, 1.58; 95% CI, 1.23–2.02). The FIELD Study[15] results suggest that fenofibrates increase mainly PE risk. Given the limited number of available studies and data, no sensitivity analysis was possible on different outcomes (PE and DVT), type of fibrates, and dosage.

Non-statin lipid-lowering drugs

Pooling data of studies reporting the risk of VTE in non-statin lipid-lowering drugs users, we found no effect on the risk of VTE (random-effects model, OR, 0.88; 95% CI, 0.72–1.07).[17,20,21,25,26] The only study investigating niacin also failed to demonstrate an effect on the risk of VTE.[14]

Discussion

This is to our knowledge the first systematic review and meta-analysis that assessed the effect of lipid-lowering drugs on the risk of VTE. The results of this study indicate that the use of statins is associated with a reduced risk of VTE and that the use

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Table 1 Baseline characteristics

Study	Patients	Objective diagnosis (diagnostic tools if specified)	Previous VTE as exclusion criteria	Study drugs	Primary or secondary prevention of CVD
Randomized Controlled Trials					
The Coronary Drug Project Research Group[14]	5011 (1103 in the clofibrate group, 1119 in the niacin group, 2789 in the placebo group)	NA	No	Clofibrate 1.8 mg daily; Niacin 3.0 mg daily; placebo	Secondary prevention
The FIELD Study Investigators[15]	9795 (4895 in the fenofibrate arm, 4900 in the placebo arm)	NA	No	Fenofibrate 200 mg daily vs. placebo in type 2 diabetes patients not taking statins	Primary and secondary prevention
JUPITER Study, 2009[16]	17 802 (8901 in each arm, rosuvastatin vs. placebo)	Yes (venogram, US, lung angiography, lung scan, CT scan)	No	Rosuvastatin 20 mg daily vs. placebo	Primary prevention
Cohort Studies					
Ray et al.[17]	125 862 in the primary cohort; 89 508 women in the secondary cohort	NA (registry code)	Yes (within 36 months)	Statins and other lipid-lowering drugs (not specified further)	NA (patients with a CV event in the last 36 months excluded)
Herrington et al.[18]	2471 postmenopausal women receiving estrogen/progesteron vs. placebo	NA	Yes	Statins (not specified further)	Secondary prevention
Smeeth et al.[19]	614 000 (59 000 with a statin treatment, 555 000 no statin treatment)	NA (registry code)	No	Rosuvastatin 0.9%; simvastatin 39.0%; atorvastatin 20.6%; pravastatin 5.3%; fluvastatin 1.0%; cerivastatin 0.5%; mixed use 32.7%	NA
Case–Control Studies					
Yang et al.[20]	84 093 patients, of whom 72 cases of idiopathic VTE (37 confirmed and 35 probable)	37/72 yes; 35/72 no	Yes	Statins and other lipid-lowering drugs (not specified further)	NA
Doggen et al.[21]	465 postmenopausal women with VTE (348 DVT, 42 PE, 75 DVT + PE) and 1962 controls	In 93% of cases (venogram, US, lung angiography, lung scan, CT scan)	Yes	Simvastatin and pravastatin; other non-statin lipid-lowering drugs	NA
Freeman et al.[23]	76 VTE cases and 152 controls	NA	No	Pravastatin	Primary and secondary prevention
Yang and Kao[25]	173 VTE cases and 546 matched controls	Yes (venogram, US, lung angiography, lung scan, CT scan)	Yes	Lipid-lowering drugs (not specified further)	NA
Huerta et al.[24]	6550 VTE cases (3544 DVT and 3006 PE) and 10 000 matched controls	NA (registry code)	Yes	Statins (not specified further)	NA
Lacut et al.[22]	677 VTE cases and 677 matched controls	Yes (US, lung scan, CT scan, lung angiography)	Yes	Statins and fibrates (not specified further)	NA
Sørensen et al.[27]	5824 VTE cases (3823 DVT and 2001 PE) (2310 unprovoked DVT and 1056 unprovoked PE) and 58240 population controls	NA (registry code)	Yes	Statins (not specified further)	NA
Ramcharan et al.[26]	4538 VTE cases (2670 DVT, 1583 PE, 285 DVT + PE) and 5914 matched controls	Yes (hospital code plus requested evidence of an objective test)	Yes	Simvastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin, other lipid-lowering drugs	NA

CT, computed tomography; CVD, cardiovascular disease; DVT, deep venous thrombosis; NA, not available; PE, pulmonary embolism; VTE, venous thromboembolism; US, ultrasonography.

Table 2 Quality assessment

Study	Study design	Consecutive patients	Control group	Follow-up Duration (months)	Lost to follow-up (%)	Quality score
Randomized Controlled Trials						
The Coronary Drug Project Research Group[14]	RCT	Yes	Yes	74	7.4% clofibrate; 10.7% niacin; 8.0% placebo	3 (medium)
The FIELD Study Investigators[15]	RCT	Yes	Yes	60	2.2	5 (high)
JUPITER study, 2009	RCT	Yes	Yes	22.8	0%	5 (high)
Cohort Studies						
Ray et al.[17]	Retrospective cohort study	Yes	Yes	13.2–16.8	NA	2 (low)
Herrington et al.[18]	Prospective inception cohort study	No	Yes	49.2	NA	2 (low)
Smeeth et al.[19]	Retrospective population- based cohort study	Yes	Yes	52.8	NA	2 (low)
Case−Control Studies						
Yang et al.[20]	Population-based retrospective case−control study	No	Yes			1 (low)
Doggen et al.[21]	Population-based case−control study	No	Yes			1 (low)
Lacut et al.[13,22]	Case−control study	Yes	Yes			2 (high)
Freeman et al.[23]	Case−control study	No	Yes			1 (low)
Huerta et al.[24]	Prospective cohort study with case−control analysis	Yes	Yes			2 (high)
Yang and Kao[25]	Case−control study	No	Yes			1 (low)
Ramcharan et al.[26]	Population-based case−control study	No	Yes			2 (high)
Sørensen et al.[27]	Population-based case−control study	Yes	Yes			2 (high)

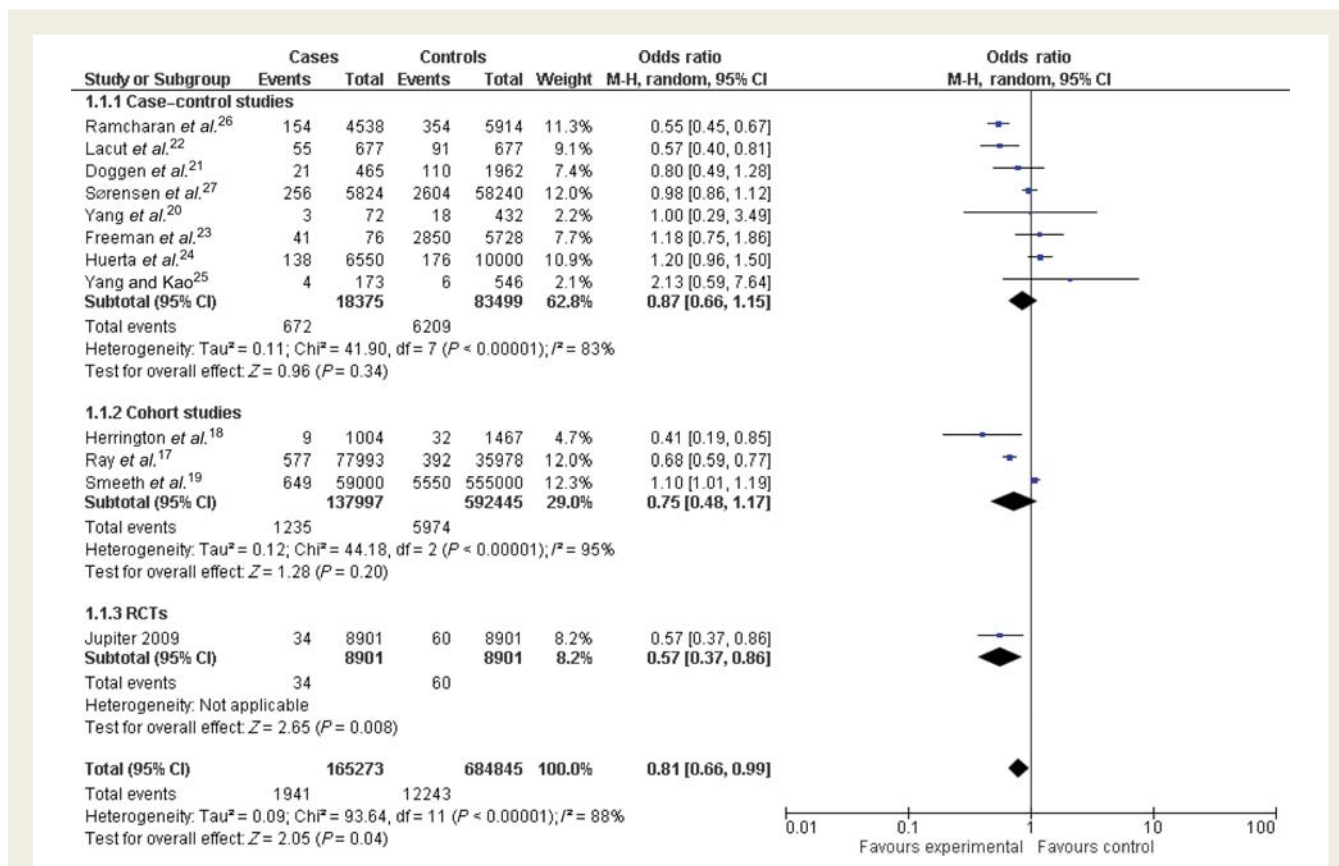NA, not available; RCT, randomized controlled trial.

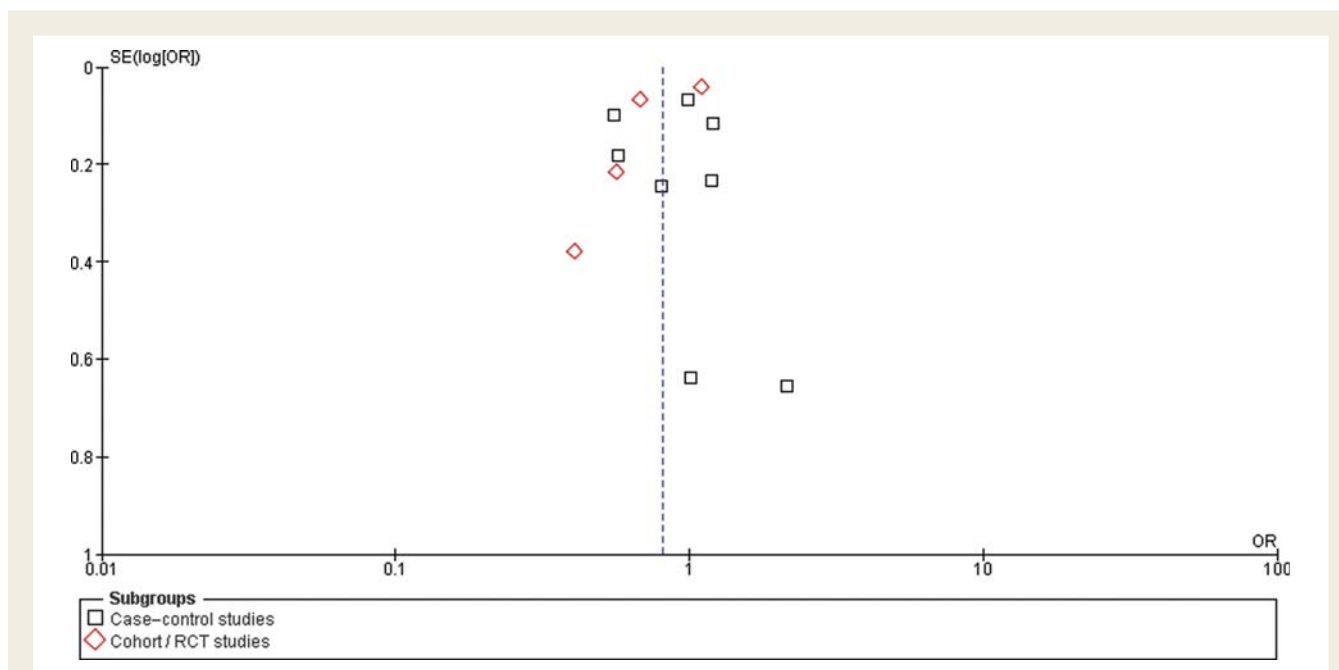**Figure 2** Odds ratio for the association between statins use and venous thromboembolism.

Figure 3 Funnel plot of studies on the association between statins use and venous thromboembolism.

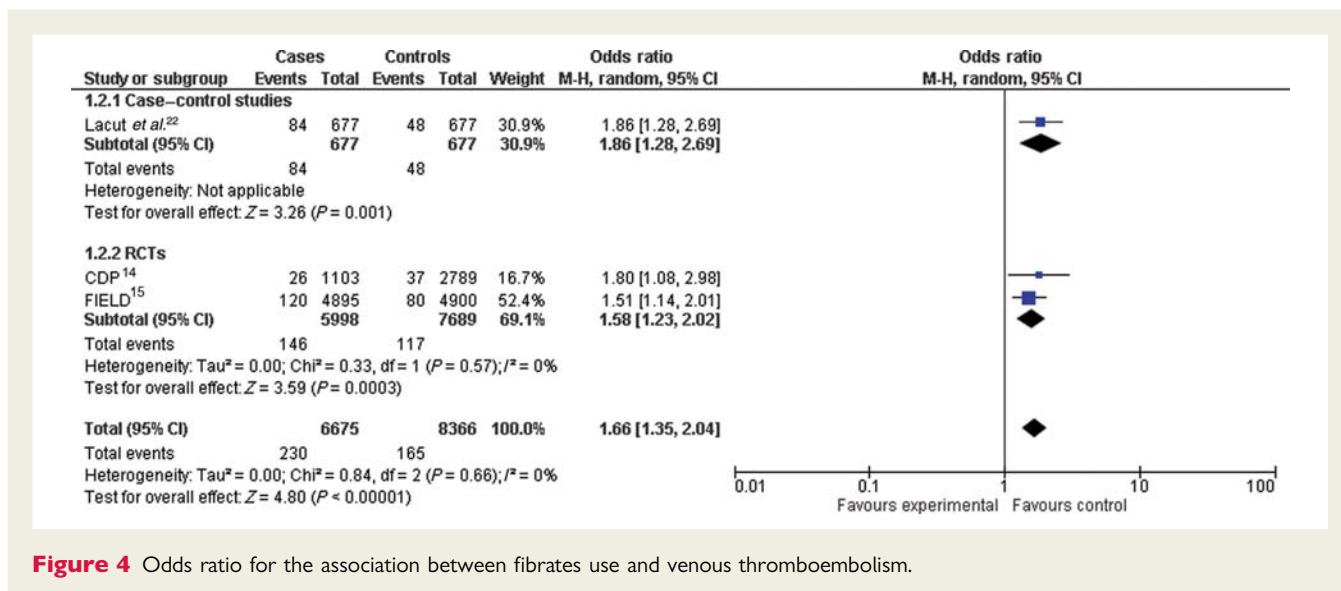| Study or subgroup	Cases Events	Total	Controls Events	Total	Weight	Odds ratio M-H, random, 95% CI
1.2.1 Case–control studies						
Lacut et al.[22]	84	677	48	677	30.9%	1.86 [1.28, 2.69]
Subtotal (95% CI)		677		677	30.9%	1.86 [1.28, 2.69]
Total events	84		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.26 (P = 0.001)						
1.2.2 RCTs						
CDP[14]	26	1103	37	2789	16.7%	1.80 [1.08, 2.98]
FIELD[15]	120	4895	80	4900	52.4%	1.51 [1.14, 2.01]
Subtotal (95% CI)		5998		7689	69.1%	1.58 [1.23, 2.02]
Total events	146		117			
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 3.59 (P = 0.0003)						
Total (95% CI)		6675		8366	100.0%	1.66 [1.35, 2.04]
Total events	230		165			
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 4.80 (P < 0.00001)						

Figure 4 Odds ratio for the association between fibrates use and venous thromboembolism.

of fibrates is associated with an increased risk of VTE. No data are available on the effects of other lipid-lowering drugs, with the exception of a single study with niacin.

Statins are the best-studied and most powerful cholesterol-lowering drugs.[1,28] Their therapeutic benefits in reducing cardiovascular risk are not completely explained by low-density lipoprotein cholesterol lowering only, thus suggesting that other mechanisms are involved.[2] Several vascular protective effects of statins have been shown: increased nitric oxide bioavailability, atherosclerotic plaque stabilization, regulation of angiogenesis, reduction of the inflammatory response, and antithrombotic properties.[2,3] Down-regulation of the blood coagulation cascade is probably the result of a decreased tissue factor expression, which leads to reduced thrombin generation.[3] In fact, statins use has been associated with the impairment of several coagulant reactions catalysed by thrombin, such as fibrinogen cleavage. Evidence indicates that statins may enhance the activity of the protein C anticoagulant pathway by increasing thrombomodulin expression on endothelial cells.[29] Inhibition of isoprenylation of signalling proteins, a covalent modification essential for their interaction with cell membranes, is the probable principal mechanism.[3] Moreover, an antiplatelet and a profibrinolytic effect of statins have been reported.[30]

All such properties of statins may support their potential effect also in the prevention of VTE. Based on the results of our meta-analysis including more than 850 000 patients, statins consistently reduce the risk of VTE by approximately 20%. This observation carries some important implications. First, there is now a clear need for a RCT primarily designed to evaluate the effects of statin use in patients at high risk for VTE, such as patients with previous VTE.[16,31] Second, VTE should now be included as a clinical endpoint in all new statins trials. Third, the claimed link between atherosclerosis and VTE appears to be reinforced.[32,33] Regardless of whether the beneficial effect of statins on the risk of VTE is simply due to lipid lowering or to their influence on thrombosis and inflammation, statins have the potential to be active on both cardiovascular and venous thromboembolic diseases.[33,34]

Fibrates, peroxisome proliferator-activated receptor-α activators, have been shown in some studies to diminish the procoagulant activity and to stimulate fibrinolysis.[35] Fibrates may also increase plasma clot permeability and susceptibility to fibrinolysis in coronary artery disease patients.[35] No relevant influence on platelet function, but increased homocysteine levels, has been reported on fibrates treatment.[22,36] Although fibrates potentially have an overall antithrombotic effect, published data suggest an increased risk for VTE. The reason for this observation remains unclear, and the increase in homocysteine levels remains the only available, albeit insufficient, explanation.[22] Well-designed *in vitro* and *in vivo* studies are thus now strongly encouraged, and also new clinical studies with fibrates should systematically include VTE events among major endpoints.

The main strengths of our review include the systematic approach, the quality assessment of the literature, and the large number of patients included. Conversely, our systematic review has several potential limitations. First, our meta-analysis was almost restricted to observational studies, mainly case–control studies, and the application of formal meta-analytic methods to observational studies is controversial, since bias implicit in the study design may misrepresent the strength of associations within the data.[7,37] However, before pooling all data together, we have provided separate analysis for cohort studies, case–control studies, and RCTs when available. The study design does not appear as the main reason for heterogeneity and the ORs from different study designs remain very similar. Second, studies included in our meta-analysis have different inclusion and exclusion criteria, and to combine results across studies may be inappropriate. However, when we repeated the analysis using a random-effects model, an approach that accounts for some of the variance between studies, we found similar results. Third, as an intrinsic limit of meta-analyses, our meta-analysis was by necessity restricted to single risk factors. Therefore, the distinct possibility exists that the strength of association may be weaker with a multifactorial regression analysis, given that it was not possible to adjust or stratify for potential confounders. In particular, the

effect of cardiovascular risk factors and a healthy user effect should be considered.[33] Fourth, given the mean low quality of the studies included in our systematic review, our findings should be interpreted with caution. In particular, all three included RCTs had VTE as a secondary outcome only. Fifth, due to limited available published data, we cannot explore whether VTE risk reduction is a class-effect or a molecule-effect of statins. Finally, since there were too few studies evaluating the effects of fibrates, the presence of publication bias could not be evaluated. Moreover, a plausible biological rationale is lacking. However, given the magnitude of the association and the homogeneity of the results in the selected studies, it is extremely unlikely that unpublished studies with different results, if really exist, could substantially modify our findings.

In conclusion, the use of statins may reduce the risk of VTE, whereas the use of fibrates may increase this risk. Before clinical implications of our findings can be discussed, RCTs evaluating the effect of statins in patients at high risk of VTE are warranted. Future prospective studies carefully investigating the underlying mechanisms of the effects of lipid-lowering drugs on haemostasis are strongly encouraged, in particular to assess the negative effects of fibrates.

Author contribution

Conception and design: A.S., M.G., E.R., W.A; data collection: A.S., M.G., E.R.; analysis and interpretation of data: A.S., F.D., P.W.K., L.G., A.V., W.A.; drafting of the manuscript: A.S., M.G., E.R.; revising it critically for important intellectual content: F.D., P.W.K., L.G., A.V., W.A.; final approval of the manuscript submitted: A.S., M.G., E.R., F.D., P.W.K., L.G., A.V., W.A.

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