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REVIEW

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A revised systematic review and meta-analysis on the effect of statins on D-dimer levels

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Abstract

Background: D-dimers are generated during endogenous fibrinolysis of a blood clot and have a central role in diagnostic algorithms to rule out venous thromboembolism. HMG-CoA reductase inhibitors, more commonly called statins, are known to have effects independent of LDL-cholesterol lowering, including antithrombotic properties. An effect of statins on D-dimer levels has been reported in a prior systematic review and meta-analysis, but methodological shortcomings might have led to an overestimated effect. To re-evaluate the association between statins and D-dimer levels, we systematically reviewed all published articles on the influence of statins on D-dimer levels and conducted a novel meta-analysis (PROSPERO registration number CRD42017058932).

Materials and methods: We electronically searched EMBASE, Medline Epub, Cochrane, Web of Science and Google Scholar (100 top relevance) (date of last search: 5 October 2017). We included randomized controlled trials, cohort studies and cross-sectional studies. Two reviewers independently screened all articles retrieved and extracted data on study and patient characteristics, study quality and D-dimer levels.

Results: Study-level meta-analysis involving 18,052 study participants showed lower D-dimer levels in those receiving statin treatment than controls (SMD: −0.165, 95% CI −0.234; −0.096, $P = <0.001$). Sensitivity analyses and additional analyses on treatment duration (<12 weeks vs ≥12 weeks) and type of statin (lipophilic or hydrophilic) did not modify this overall result.

Conclusion: This meta-analysis suggests an association between use of statins and reduction of D-dimer levels, independent of treatment duration and type of statin used. This effect is small but robust, and should be interpreted with caution.

KEYWORDS
D-dimer, fibrin fragment D, hydroxymethylglutaryl-CoA reductase inhibitors, meta-analysis, venous thromboembolism

1 | INTRODUCTION

In case of a thromboembolism, D-dimers are generated in the blood clot during fibrinolysis by the sequential action of thrombin, activated factor XIII and plasmin.[1,2] Age, active malignancy, infection, pregnancy and use of anticoagulants are well known to have an influence on D-dimer levels.[3-6] Use of medication with an effect on thrombus formation, such as HMG-CoA reductase inhibitors, more commonly known as statins, may influence D-dimer levels as well. These antithrombotic properties are part of what has been referred to as the cholesterol-independent or "pleiotropic" effects of statins, explaining why the benefits observed with statins appear to exceed what might be expected from changes in cholesterol levels alone.[7-9] In line with these antithrombotic effects, statin treatment might lead to a 15% lower risk of primary venous thrombosis as confirmed in a recent meta-analysis of intervention studies.[7]

In clinical practice, D-dimer levels have a central role in diagnostic algorithms to rule out venous thromboembolism (VTE).[10,11] Several studies have addressed the effect of statins on D-dimer levels, with some of them being evaluated in a systematic review and meta-analysis by Sahebkar et al[12] This meta-analysis included nine randomized controlled trials and reported a significant reduction of 0.988 μg/mL (95%CI: −1.590 to −0.385, $P = 0.001$) in D-dimer levels in statin users. However, this estimate is inappropriate since the used Cohen's d effect size should be dimensionless, while 0.988 μg/mL suggests a tremendous clinical impact of statin use on D-dimer levels. Triggered by this inaccuracy, we further elucidated the used methods and results and found several important shortcomings. Our main concerns next to misuse of Cohen's d are incorrect extraction of data from original studies and unreported assumptions.

Because the research question is of high importance though, we decided to conduct a novel systematic review and meta-analysis on the effect of statins on D-dimer levels, including recent studies.

2 | METHODS

2.1 | Protocol registration

This study was registered on 10 March 2017 in the PROSPERO international prospective register of systematic reviews (CRD42017058932) and designed according to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Appendix S1 and S2).[13]

2.1.1 | Search methods for identification of studies

Together with a biomedical information specialist (see Acknowledgement), SS-G electronically searched the following databases: EMBASE (Ovid SP); Medline Epub (Ovid SP); Cochrane Central Register of Controlled Trials (CENTRAL); Web of Science and Google Scholar (100 top relevance) (date of last search: 5 October 2017). We used search terms as reported in "Appendix S3," in summary: D-dimer OR D-dimers AND statin OR statins OR hydroxymethylglutaryl reductase OR HMG-CoA reductase in combination with individual drug names of statins. To improve sensitivity, we also combined these search terms with the wild-card term "*" and the accessory MeSH terms.

2.2 | Data collection and extraction process

Two authors (SS-G and FM) independently screened titles and abstracts retrieved by the electronic survey, and disagreement in selection was resolved by discussion. After consensus was reached, the two reviewers independently selected eligible articles based on the results in full text. Selection of articles was discussed in detail, and in case of disagreement, a third author (TvG) was consulted for final decision. We present a flow diagram to show the decision-making process for including studies in the review (Figure 1).[13] The first reviewer (SS-G) extracted the following data: first author's name, year of publication, study design, country where the study was performed, D-dimer assay used, use of co-medication, number of participants, time of exposure, statin regimen, D-dimer levels with its variation and the conclusions of the individual studies on the effect of statins on the D-dimer levels. Also, all QUADAS-2 items were assessed. If results could not be extracted from original articles (table or well described in the text), authors were requested repeatedly to send their original data. All D-dimer levels were converted to μg/mL. If multiple D-dimer levels were available, we chose to report those values close to 6-month follow-up. All results after extraction were double-checked and confirmed by the second reviewer (FM).

2.3 | Selection of studies

We included randomized controlled trials, cohort studies and cross-sectional studies conducted in humans, in which D-dimers levels were described or reported and results could be compared among users or nonusers of statins. For both randomized controlled trials and cohort studies, we defined that statins should be used for at least 7 days in order to achieve a pharmacodynamically relevant effect.[14,15] Also, to prevent interference of the effect of anticoagulant

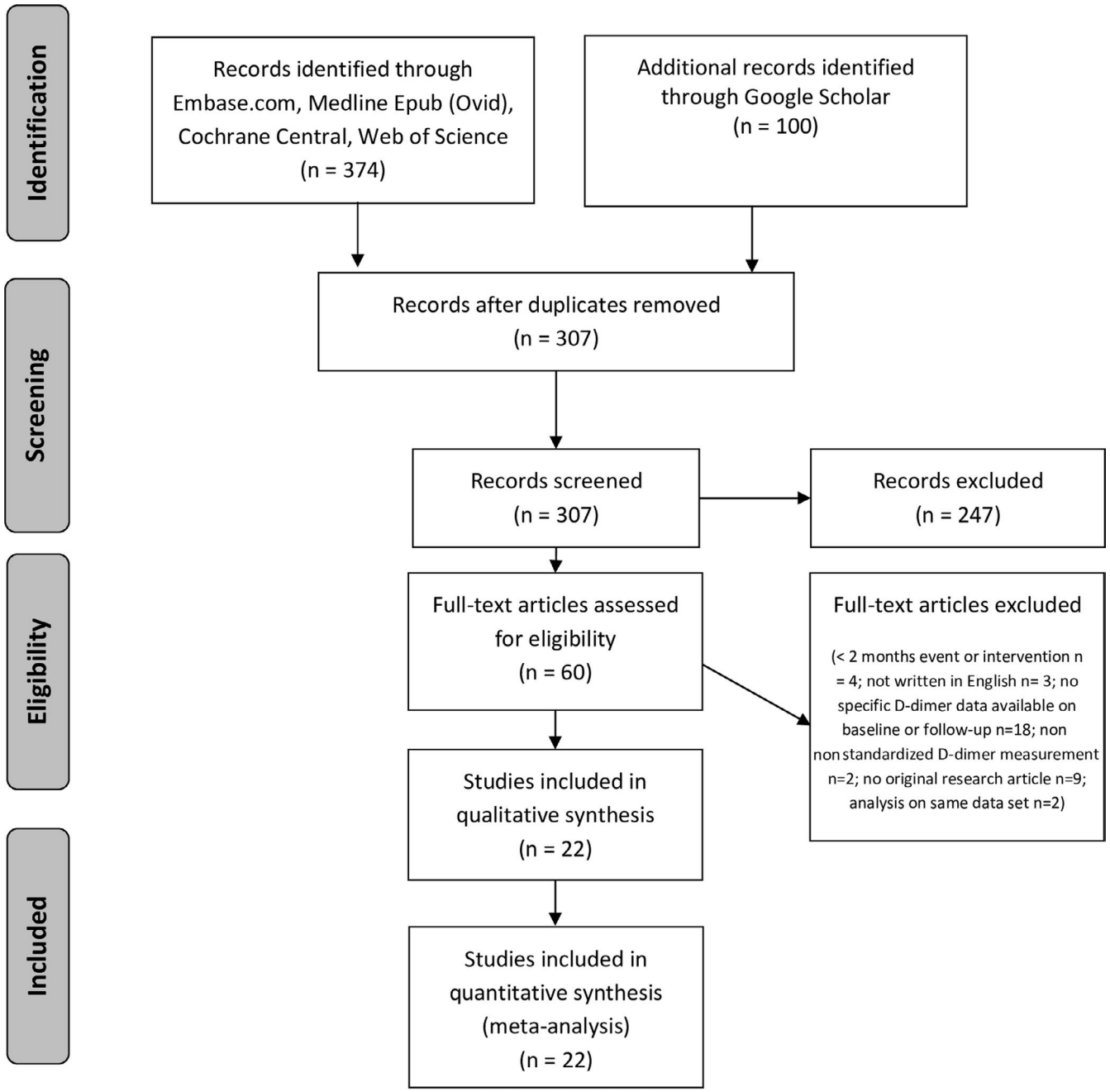


FIGURE 1 Flow diagram on decision-making process for including studies following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement

drugs on D-dimer levels, we excluded randomized controlled trials or cohorts primary conducted among patients treated with anticoagulant drugs at baseline or during follow-up. Studies in which any medical intervention or cardiovascular event within 2 months between baseline and follow-up measurement of D-dimer levels was part of the inclusion criteria were also excluded to reduce confounding effects on D-dimer levels. Since different D-dimer tests are used in clinical practice, we decided to include only standardized enzyme-linked immunoassays or latex (semi) quantitative tests.[16] Studies without availability of full text that were also not available after repeated requests to the (corresponding) authors or articles not written in English language were excluded, because the quality of these articles could not be assessed.

2.4 | Risk of bias in individual studies and across studies

The data extraction form incorporated a quality assessment section comprising items from Quality Assessment of

Diagnostic Accuracy Studies-2 (QUADAS-2).[17] Following this revised tool, we omitted and added signalling questions and two independent reviewers (SS and FM) applied the QUADAS-2 score in a small number of studies. After refinement of the tool (as described in detail in Appendix S4) with review-specific signalling questions and appropriate items, grouped into three domains (patient selection, index test, and flow and timing) also scoring conflicts of interest, we applied this tool for all studies. We evaluated the influence of each study on the overall effect size by removing one study each time and repeating the analysis, a so-called leave-one-out method sensitivity analysis.[18] We also performed a subanalysis including only studies with low-risk patient selection bias and low concern about applicability according to the scoring of these QUADAS-2 items and performed a separate subanalysis only including controlled trials. To detect potential publication bias, we visually inspected the distribution of the studies within a funnel plot and also created a funnel plot taking into account the trim-and-fill adjustment of Duval and Tweedie.[19] Also, Begg's rank correlation and Egger's test were used to detect publication bias.[20,21] Furthermore, as another marker of publication bias, we estimated the number of missing studies we would need to retrieve and impute in the meta-analysis to make the p-value nonsignificant using the "fail-safe N" method.[22]

2.5 | Quantitative data-synthesis

The meta-analysis was conducted using Comprehensive Meta-analysis (version 3; Biostat). In studies in which participants were exposed to different statin regimens, the different statin-exposed groups were analysed separately and values were compared to the control group in case of (randomized) controlled studies. When medians and interquartile ranges (IQR) were reported, we estimated the average standard deviation (SD) using the following formula: SD = ((75th percentile-25th percentile)/1.35) and in case of reporting medians and full range, we estimated the average SD using the following formula: SD = ((75th percentile-25th percentile)/5.16).[23] If not reported, the mean difference was estimated using the following formula: SD = square root [(SDpre-treatment)2 + (SDpost-treatment)2 − (2R × SDpre-treatment × SDpost-treatment)], assuming a correlation coefficient (R) = 0.5. Net changes in measurements (change scores) were calculated for controlled trials, as follows: (value at end of follow-up in the treatment group − value at baseline in the treatment group) − (value at end of follow-up in the control group − value at baseline in the control group). If percentage change in D-dimer levels was reported, we estimated mean or median D-dimer post-treatment levels by multiplying reported mean or median pre-treatment D-dimer levels with 1 + percentage change and assumed that the post-treatment SD was equal to reported SD before treatment. For crossover studies, we used the reported results of delta mean change and its corresponding SD to prevent artificial widening of confidence intervals of the pooled treatment effect.[24] For cohorts, we calculated change scores by (value at end of follow-up in the treatment group − value at baseline in the treatment group) assuming that in a fictional control group D-dimer would not change during follow-up. For results on cross-sectional studies, we measured change scores by (value in the statin users group − value in the nonexposed group). When the authors adjusted D-dimer levels for other confounding factors, we used the adjusted D-dimer levels for analysis. We expressed effect sizes as a standardized mean difference (SMD) with its corresponding 95% confidence intervals (CIs) using the dimensionless Cohen's d as the summary statistic.[25] To compensate for heterogeneity including study design, population characteristics, statin dose and treatment duration, we used a random-effects model. Post hoc subanalyses were performed to assess the potential effects of treatment duration of statin therapy (<12 weeks vs ≥12 weeks) and type of statin (lipophilic or hydrophilic). Simvastatin, atorvastatin and fluvastatin were classified as lipophilic statins and pravastatin and rosuvastatin as hydrophilic statins.[15]

3 | RESULTS

3.1 | Study selection and evaluation of bias of individual studies

In total, we screened 307 studies, of which 60 were assessed for eligibility reading full text, and finally, 22 studies were included in this review (Figure 1).[26-47] Reasons for exclusion were an event or intervention <2 months (n = 4), not written in English (n = 3), no specific D-dimer data available on baseline or follow-up (n = 18), nonstandardized D-dimer measurement (n = 2), no original research article (n = 9) and repeated analysis on same data set (n = 2). We included 7 controlled trials, 11 cohort studies and 4 cross-sectional studies. Taken together, this analysis included 22 control groups and 27 statin-exposed groups with a total number of 18 052 study participants (Table 1). The included studies were performed among different study populations. Six studies were performed in subjects with dyslipidaemia, 6 studies in patients with proven cardiovascular disease, 4 studies in HIV-infected patients, 2 in patients with type 2 diabetes mellitus, one in healthy subjects, one in patients diagnosed with lupus, one in COPD patients and one in heart transplant patients. Of all 27 statin-exposed groups, 17 groups were defined as lipophilic-type statin users and 7 as hydrophilic-type statin users, while the other 3 groups comprised of lipophilic-type as well as hydrophilic-type statin users. Of the

23 statin-exposed groups in which we could assess treatment duration, 19 groups were exposed to statins for 12 weeks or longer.

The risk of bias regarding patient selection was regarded low for only 6 of the 22 included studies and for 8 studies we had concerns about applicability of the results based on the specific characteristics of the statin-exposed groups and control groups included in these studies (Figure 2, Table S1). For four studies, the D-dimer test was not clearly described, and we assumed a standardized test.[34,37,38,47]

3.2 | Meta-analysis

Study-level meta-analysis involving 18 052 study participants showed significantly lower D-dimer levels in those receiving statin treatment compared to controls (SMD: −0.165, 95% CI −0.234; −0.096, $P \leq 0.001$) (Figure 3). The estimated effect sizes were similar in sensitivity analyses that omitted any single study (Figure 4). The 6 studies with low risk of patient selection (SMD: −0.099, 95%CI −0.140; −0.058, $P < 0.001$) and the 16 studies with low risk of limited patient applicability (SMD: −0.216, 95%CI −0.334; −0.099, $P < 0.001$) also resulted in lower D-dimer values after statin treatment. A separate meta-analysis of the 7 controlled trials did not show a different effect on D-dimer levels (SMD: −0.096, 95% CI −0.138; −0.055, $P < 0.001$). Furthermore, treatment duration (<12 weeks vs ≥12 weeks) did not influence the effect on D-dimer levels in statin users ($P = 0.887$) (Figure 5) and type of statin (lipophilic or hydrophilic) also did not modify this overall result ($P = 0.167$) (Figure 6).

3.3 | Publication bias

A visual inspection of the funnel plot showed asymmetry, suggesting potential publication bias. Using the "trim-and-fill" method with five potentially missing studies imputed, the effect size was estimated to an adjusted SMD with a larger effect (−0.224, 95% CI −0.295; −0.153) than the unadjusted SMD (Figure 7). Begg's rank correlation (Kendall's Tau with continuity correction = −0.160, $Z = 1.167$, two-tailed $P = 0.243$) and Egger's test (intercept −0.611, 95% CI −1.447; 0.226, two-tailed $P = 0.145$) were both nonsignificant. Following the "fail-safe N" method, we would need to retrieve and impute 422 missing studies in the meta-analysis to make the p-value nonsignificant.

4 | DISCUSSION

In this meta-analysis, for which we included randomized controlled trials, cohort and cross-sectional studies conducted in humans, we found that statin treatment is associated with lower D-dimer levels. This effect is small but robust and not driven by any single study. Results from post hoc subanalyses on treatment duration and type of statin therapy were not different from this overall effect.

Our findings are important in further understanding the pleiotropic antithrombotic effects of statins. Statins have been shown to significantly lower the risk of primary VTE and therefore might have a role in the prevention of VTEs.[7,48] Several mechanisms have been described to explain these antithrombotic properties. Statins inhibit platelet activation within hours after intake by upregulation of the nitric oxide synthase and downregulation of phospholipase A2–mediated thromboxane A2 formation and probably also by reduced exposure of platelet-derived microparticles and glycoprotein IIIa, a receptor for fibrinogen and von Willebrand factor.[49-51] Also important, statins interfere directly with the clotting system. In vitro, two lipophilic types of statins decreased tissue factor activity in a dose-dependent manner.[52] As a result, a smaller amount of factor X is activated and generation of thrombin is diminished.[8,53,54] Other ways through which statins interfere with the clotting system are inhibition of isoprenoid intermediates, which indirectly activates the protein C pathway and lowering of the oxidized LDL-induced tissue factor expression. Inhibition of geranylgeranylation of the Rho/Rho kinase pathway is one of the key mechanisms of these anticoagulant effects.[8,55] By inhibition of this pathway, resulting in a shift in the fibrinolytic balance towards increased fibrinolytic activity is suggested by inhibition of the expression of plasminogen activator inhibitor-1 and upregulation of tissue-type plasminogen activator.[56,57]

These mechanisms might consequently result in lower D-dimer levels in statin users. This decrease of D-dimer levels may theoretically be stronger for lipophilic than for hydrophilic type of statin users. Lipophilic type of statins can enter cells in any organ and also penetrate cell membranes. In contrast, cellular uptake of hydrophilic type of statins is dependent on the presence of a specific carrier-mediated mechanism, which is only present in hepatocytes but not in extrahepatic cells.[58] Furthermore, tissue factor activity could in vitro only be decreased by lipophilic type of statins and not by pravastatin, a hydrophilic type of statin.[52] Clinical relevant difference of pleiotropic effects in general between lipophilic and hydrophilic type of statins is however controversial.[9] In our subanalyses on type of statin therapy, for both lipophilic and hydrophilic type of statin users D-dimer levels were significantly lower. This effect was not significantly different among these groups. Probably the clinical anticoagulant effect in vivo is independent on the mechanism of uptake.

The question of a possible dose-effect of statins in lowering D-dimer levels is also relevant, yet hard to answer because of difference in statin types and dosages that were applied in the included studies. Still, we applied a post hoc analysis, utilizing the previously developed concept of a "statin

TABLE 1 Characteristics of included studies for meta-analysis on the effect of statins on plasma D-dimer level

	Location	Population	D-dimer assay	Information about use of co-medication	Age (years)	Time of exposure
Controlled trials						
Chang, 2002	South Korea	Haemodialysis patients with hypercholesterolaemia5	ELISA Asserachrom D-Di (Diagnostica Stago, Asnières-sur-Seine, France)	Exclusion cholesterol modifying or oxidation medication	63 (11) 60 (12)	8 wk
Eckhard, 2014	USA	Nonhypercholesterolaemic HIV infected	LPIA (Diagnostica Stago, Parsippany, NJ)	On antiretroviral therapy ASA, steroids, NSAIDs, antihypertensive medication	45.6 (41.1-51.4) 46.9 (39.2-53.6)	24 wk
Kinlay, 2009	USA	acute coronary syndromes	Not reported	ASA, heparin, nitrates and β-blockers	64 (12)	16 wk
Nixon, 2016[a]	USA	HIV infected	ELISA (Diagnostica Stago, Asnières-sur-Seine, France)	On antiretroviral therapy Exclusion of immunosuppressant users	48 (41-55)	20 wk
Sommeijer, 2004	The Netherlands	Type 2 diabetes mellitus	LPIA (bioMérieux, Durham, NC)op	Antihypertensive medication, ASA	Overall: 59 (54-64) median (IQR)	8 wk
Tonkin, 2015	Australia	Acute coronary syndrome	LPIA (Architect c8000, Abbott Diagnostics)	ASA	62 (55-67) 63 (56-68)	12 mos
Van de Ree, 2003	The Netherlands	Type 2 diabetes mellitus	ELISA (Dade-Behring, Marburg, Germany)	-	59.7 (7.6) 60.3 (7.8) 58.6 (7.5)	30 wk
Cohort studies						
Bolaman, 2006	Turkey	Primary hypercholesterolaemia	ELISA (not otherwise specified)	-	55 (10)	24 wk
Calza, 2017	Italy	HIV-1 infected	ELISA (Medical Systems, Genova, Italy)	On antiretroviral therapy Exclusion of steroid, androgen, oestrogen, growth hormone, antihypertensive medication, thyroid preparation and acid-reducing agent users	46.8 (40.6-55.9)	6 mos
Costejon, 2017	Spain	Females with sae systemic lupus erythematosus	Not reported	Antimalarials and immunosuppressant	47 (23-80)	8 wk
Hölschermann, 2000	Germany	heart transplant recipients receiving oral immunosuppression	ELISA (Asserachrom; Boehringer Mannheim Diagnostics, Mannheim, Germany)	immunosuppresssants	48 (12) (mean (SD))	7 d or 1 mos
Joukhadar, 2001	Austria	Hypercholesterolaemia	ELISA (Diagnostica Stago, Asnières, France)	Exclusion of hypolipaemic, anticoagulant, anti-inflammatory or antihypertensive medication users	55 (9) 52 (9) 55 (8)	3 mos
Lin, 2000	Taiwan	hypercholesterolaemia	LPIA (Diagnostica Stago, France)	Antihypertensive medication, hormone replacement	59.8 (7.1)	8 wk
Lin, 2006	Taiwan	hyperlipidaemia	LPIA (Diagnostica Stago, France)	-	58.5 (9.7)	16 wk
Seljeflot, 2002	Norway	dyslipidaemia and history of angina pectoris	ELISA in plasma and serum (Asserachrom D-Di; Stago Diagnostica, Asnières-sur-Seine, France)	Antihypertensive medication, warfarin, ASA, nitrates	Not reported	12 mos
Trifiletti, 2003	Italy	Hypercholesterolaemia	ELISA (Asserachrom; Diagnostica Stago)	Exclusion of ASA users	55 (3)	6 mos

Regimen (daily dose)	Participants (number)	D-dimer (μg/mL) before exposure	D-dimer (μg/mL) after exposure	Conclusion	Details
Simvastatin (20mg) No simvastatin	28 30	1.05 (0.90) 1.12 (1.01)	0.99 (0.83) 1.09 (0.97)	No effect	Open RCT
Rosuvastatin (10 mg) Placebo	67 69	0.19(0.13-0.33) 0.18 (0.09, 0.29)	Baseline + 6.9% (43.8 to −35.0) Baseline + 21.9% (−9.1 to 73.3)	No effect	Double-blind RCT
Atorvastatin (80 mg) Placebo	387	Overall 0.3447 (0.0708 to 5.351)	Baseline + 0.0108 μg/mL (−93,2 to 145) Baseline + 0.0244 μg/mL (−0.1097 to 0.1234)	No effect	Double-blind RCT
a)Atorvastatin (10-20 mg) a)Placebo b)Placebo b)Atorvastatin (10-20mg)	37 37 36 36	0.1870 (0.1209-0.3196) 0.1998 (0.1319-0.3383) 0.1785 (0.1256-0.2545) 0.1727 (0.1212-0.3039)	0.219 (0.1352-0.3177) 0.2127 (0.1467-0.3393) 0.1804 (0.1316-0.2250) 0.1755 (0.1113-0.2387)	No difference	Double-blind RCT with crossover design with 4-wk washout period
Pravastatin (40 mg) No pravastatin	50 50	-	Between pravastatin and no pravastatin group change: −0.02 (−0.09 to 0.05)	No effect	Open RCT met crossover design.
Pravastatin (40mg) Placebo	3941 3922	0.172 (0.112-0.269) 0.173 (0.112-0.276)	0.166 (0.108-0.263) 0.178 (0.115-0.284)	Significant reduction	Double-blind RCT
a)Atorvastatin (10 mg) b)Atorvastatin (40-80 mg) Placebo	69 66 61	0.115 (0.086-0.160) 0.137(0.104-0.186) 0.123 (0.101-0.151)	Baseline −7.4% Baseline −8.5% Baseline + 1.9%	Significant reduction in both atorvastatin groups	Double-blind RCT
Atorvastatin (10mg – 20mg)	44	0.195(0.073)	0.197 (0.085)	No effect	
rosuvastatin (10mg)	57	0.345 (0.166-0.445)	0.275 (0.149-0.381)	Significant reduction	
Atorvastatin (20mg)	37	0.49 (0.46)	0.51 (0.39)	No effect	
Simvastatin (10mg)	15	0.695 (total range 0.160-1.580)	0.490 (total range 0.160-1.470)	Significant reduction	
a) Atorvastatin (10 mg) b) Pravastatin (40 mg) c) Simvastatin (40 mg) Pooled data	24 24 27 75	0.42 (0.53) 0.29 (0.15) 0.35 (0.25) 0.35(0.34)	0.35 (0.34) 0.29(0.16) 0.33(0.17) 0.33(0.23)	No effect	
Fluvastatin (40mg)	23	0.38 (0.31)	0.28 (0.19)	Significant reduction	Exclusion of familial hypercholesterolaemia
Simvastatin (20mg-40mg)	22	0.33 (0.17)	0.29 (0.14)	No effect	
a) atorvastatin (20-40mg) b) Simvastatin (20-40mg)	28 30	0.493 (0.296-0.767) 0.384(0.218-0.657)	0.416 (0.269-0.749) 0.385(0.221-0.541)	No effect	Both serum and plasma D-dimers reported. In this review, plasma D-dimer (mostly used assay) reported
Atorvastatin (20mg)	32	0.248 (0.055)	0.229 (0.042)	No effect	

(Continues)

TABLE 1 (Continued)

	Location	Population	D-dimer assay	Information about use of co-medication	Age (years)	Time of exposur
Wada, 1992	Japan	Hypercholesterolaemia	Felisa D-dimer (Agen, Brisbane, Australia)	-	55.2 (14.6)	>3 mos
Weiss, 2016	France	HIV-1–infected receiving c-ART	ELISA (Asserachrom D-Di)	c-ART	47 (41-54)	12 wk
Cross-sectional studies						
Adams, 2013	USA	Caucasian, African American, Hispanic and Chinese, free of cardiovascular diseases or active cancer	LPIA(Liatest D-DI; Diagnostica Stago, Parsippany, NJ)	-	65.9 (8.7) 61.5 (10.3)	-
Kaba, 2004	USA	≥2 months post-myocardial infarction	ELISA (American Diagnostica, Greenwich, CT, USA)	ASA, antihypertensive medication, oral anticoagulants	60 (12) 58 (11)	-
Vidula, 2010	USA	Peripheral artery disease	ELISA (Asserachrom D-Di kit; Diagnostica Stago, Asnières-sur-Seine, France)	-	72.1 (7.9) 73.0 (8.9)	
Walter, 2010	Germany	Undergoing elective coronary angiography	ELISA (Asserachrom D-Di, Stago, Asnières, France)	Antihypertensive medication, oral antihyperglycaemic drugs, ASA, clopidogrel	60.6 (10.4) 62.4 (9.0)	-

Note: Data are reported as means (SD) or medians (75th percentile to 25th percentile) unless stated otherwise

Abbreviations: ASA, acetylsalicylic acid; d, days; ELISA, enzyme-linked immunosorbent assay; LPIA, latex-enhanced photometric immunoassays; mg, milligram; mos, months; NA, not available; RCT, randomized controlled trial; wk, weeks.

[a]Original data on effects on D-dimers received and reported.

correction factor," while adjusting for differences in the potency of statin type/dosage on LDL lowering.[59] Following this concept, we visually inspected the relation of the SMD in D-dimer levels against the statin correction factor and found no clear dose-effect relation (Figure S1). An explanation for this lack of dose-effect on D-dimer levels could be that other mechanisms are involved in the anticoagulant effect of statins compared to the cholesterol-dependent effects. The dose-effect relation of statins on D-dimers levels might therefore be independent of the potency of lowering LDL-cholesterol levels.

Considering lower D-dimer levels in statin users, the performance of the diagnostic algorithms used for patients with suspected pulmonary embolism or deep vein thrombosis could be different for statin users. In these algorithms, a normal D-dimer level in combination with a low clinical probability of thrombosis safely excludes VTE.[60,61] Most D-dimer cut-offs in these diagnostic algorithms range between 0.5 and 1.0 μg/mL,

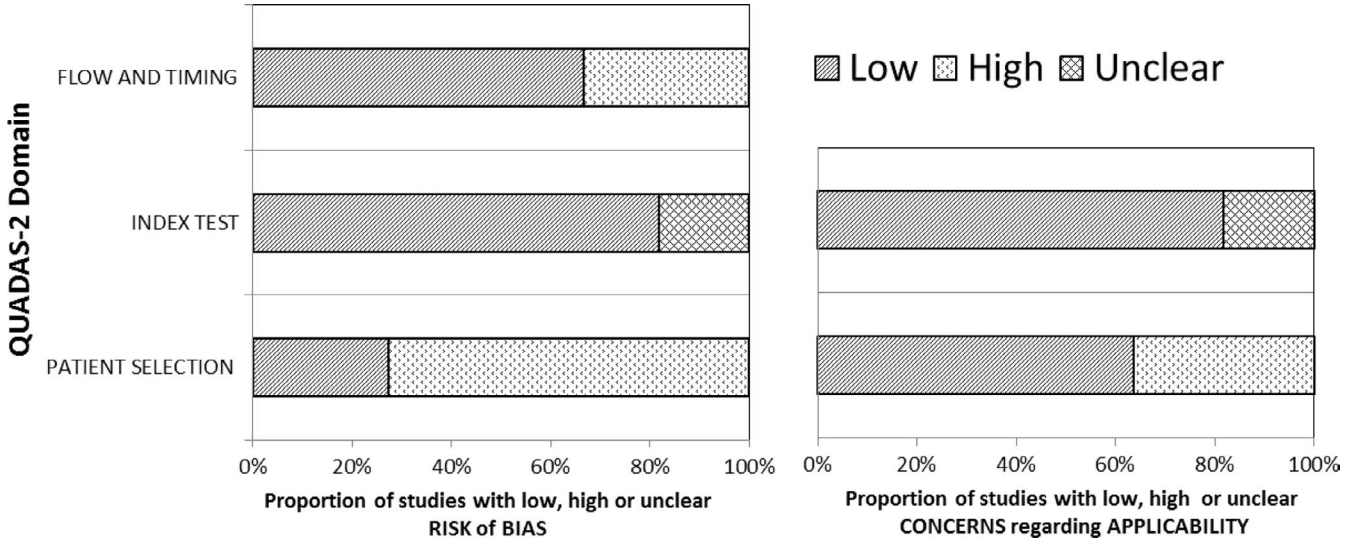


FIGURE 2 Graphical display for QUADAS-2 results of the 22 studies included

Regimen (daily dose)	Participants (number)	D-dimer (μg/mL) before exposure	D-dimer (μg/mL) after exposure	Conclusion	Details
Pravastatin (10mg)	48	0.11 (0.06)	0.056 (0.039)	Significant reduction	
Rosuvastatin (20 mg)	43	0.194 (0.147-0.279)	Baseline +3.7% (−18.2 to +23.3)	No effect	
Statin users Nonusers	1001 5786	Not reported	0.21 0.23	Significant reduction	Adjustment for age, sex, education, individual income and cardiovascular risk factors
Statin users Nonusers	644 401	0.487 (0.434) 0.731 (1.2)	-	Significant reduction	
Statin users Nonusers	242 337	1.1 (1.4) 0.97 (1.4)	-	No effect	
Atorvastatin (10-40mg) Nonusers	54 54	0.466 (0.173) 0.454 (0.182)	-	No effect	Matching based on the cholesterol levels

depending on the clinical rule applied.[61,62] These cut-off levels have high sensitivity rates, and therefore, a false negative test in statin users is unlikely to occur. In a recent retrospective post hoc analysis, adjusting D-dimer cut-offs for statin users did not result in a safer diagnostic strategy.[63] However, further validation in a larger prospective cohort is needed.

It is important to note that there are main differences between our methodology and the systematic review and

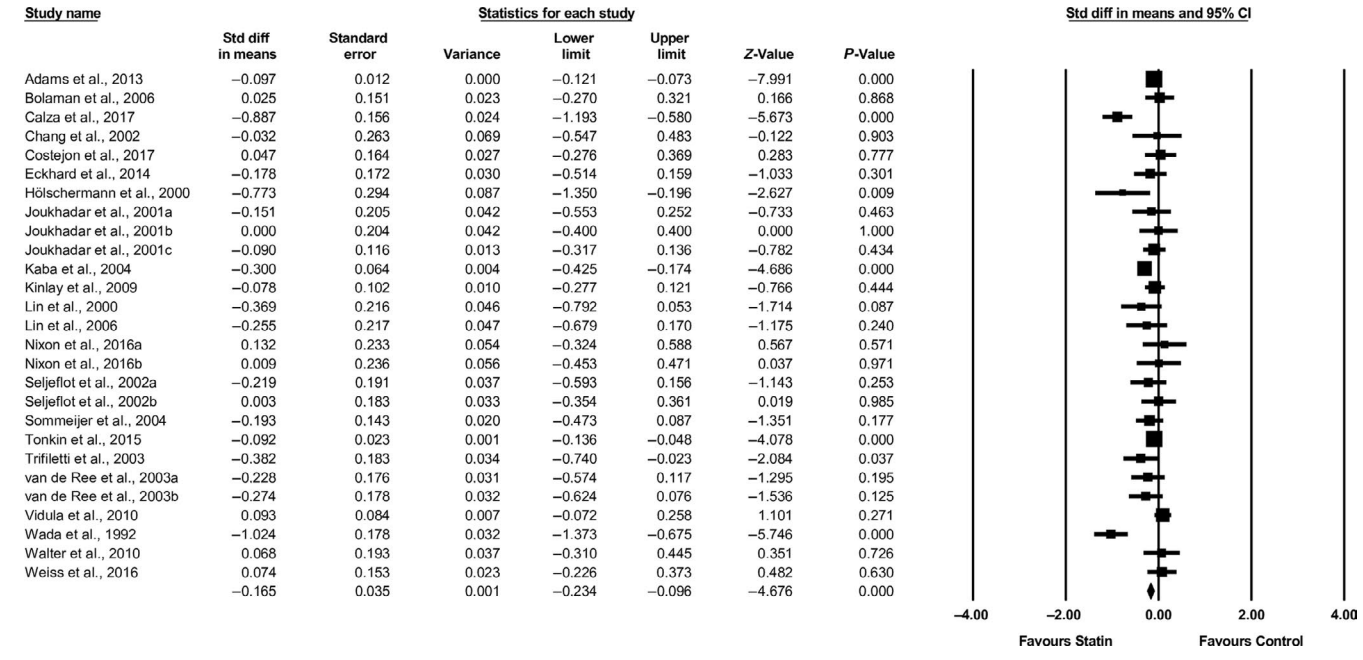


FIGURE 3 Forest plot for the effect of statin therapy on plasma D-dimer concentrations. Effect sizes were expressed as standardized mean difference (SMD) with its corresponding 95% confidence intervals (CIs) using Cohen's d as the summary statistic. A random-effects model was used for performance of the meta-analysis

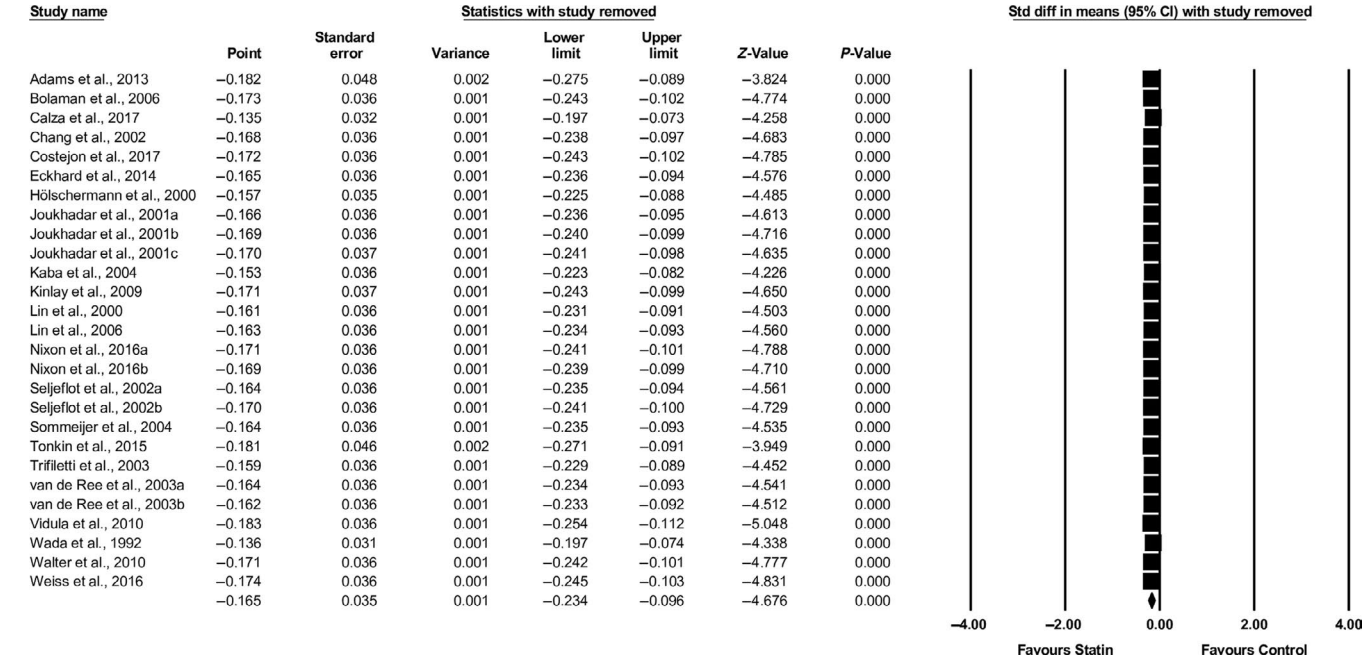


FIGURE 4 Leave-one-out sensitivity analysis of the effect of statin therapy on D-dimer

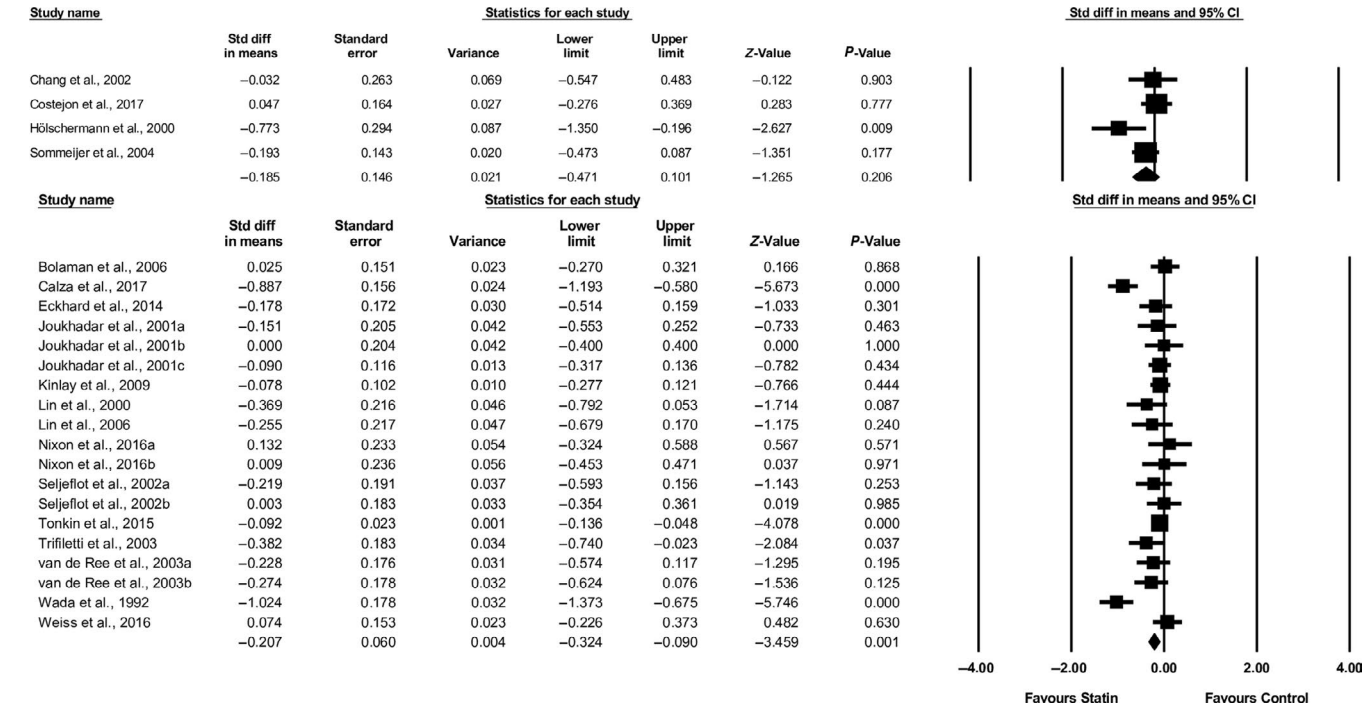
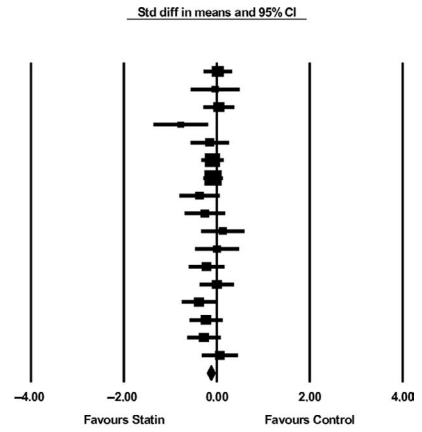


FIGURE 5 Forest plot of the effect of statin therapy on D-dimer with treatment durations of < 12 weeks (above) and > 12 weeks (below). Effect sizes were expressed as standardized mean difference (SMD) with its corresponding 95% confidence intervals (CIs) using Cohen's d as the summary statistic. A random-effects model was used for performance of the meta-analysis

meta-analysis by Sahebkar et al (2). First, in both studies effect sizes are expressed as standardized mean difference (SMD) using Cohen's d. However, Cohen's d is a dimensionless quantity, calculated as the ratio of the difference between the means of two samples and their pooled standard deviation. Thus, Cohen's d can be interpreted as a standardized difference.[64] Cohen's d was developed to compare effects across studies (even) when outcome variables vary, and results could be interpreted by referring to benchmarks with small (Cohen's d = 0.2), medium (0.5) and large (0.8)

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value
Bolaman et al., 2006	0.025	0.151	0.023	−0.270	0.321	0.166	0.868
Chang et al., 2002	−0.032	0.263	0.069	−0.547	0.483	−0.122	0.903
Costejon et al., 2017	0.047	0.164	0.027	−0.276	0.369	0.283	0.777
Hölschermann et al., 2000	−0.773	0.294	0.087	−1.350	−0.196	−2.627	0.009
Joukhadar et al., 2001a	−0.151	0.205	0.042	−0.553	0.252	−0.733	0.463
Joukhadar et al., 2001c	−0.090	0.116	0.013	−0.317	0.136	−0.782	0.434
Kinlay et al., 2009	−0.078	0.102	0.010	−0.277	0.121	−0.766	0.444
Lin et al., 2000	−0.369	0.216	0.046	−0.792	0.053	−1.714	0.087
Lin et al., 2006	−0.255	0.217	0.047	−0.679	0.170	−1.175	0.240
Nixon et al., 2016a	0.132	0.233	0.054	−0.324	0.588	0.567	0.571
Nixon et al., 2016b	0.009	0.236	0.056	−0.453	0.471	0.037	0.971
Seljeflot et al., 2002a	−0.219	0.191	0.037	−0.593	0.156	−1.143	0.253
Seljeflot et al., 2002b	0.003	0.183	0.033	−0.354	0.361	0.019	0.985
Trifiletti et al., 2003	−0.382	0.183	0.034	−0.740	-0.023	−2.084	0.037
van de Ree et al., 2003a	−0.228	0.176	0.031	−0.574	0.117	−1.295	0.195
van de Ree et al., 2003b	−0.274	0.178	0.032	−0.624	0.076	−1.536	0.125
Walter et al., 2010	0.068	0.193	0.037	−0.310	0.445	0.351	0.726
	−0.119	0.042	0.002	−0.202	-0.036	−2.817	0.005



Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value
Calza et al., 2017	−0.887	0.156	0.024	−1.193	−0.580	−5.673	0.000
Eckhard et al., 2014	−0.178	0.172	0.030	−0.514	0.159	−1.033	0.301
Joukhadar et al., 2001b	0.000	0.204	0.042	−0.400	0.400	0.000	1.000
Sommeijer et al., 2004	−0.193	0.143	0.020	−0.473	0.087	−1.351	0.177
Tonkin et al., 2015	−0.092	0.023	0.001	−0.136	−0.048	−4.078	0.000
Wada et al., 1992	−1.024	0.178	0.032	−1.373	−0.675	−5.746	0.000
Weiss et al., 2016	0.074	0.153	0.023	−0.226	0.373	0.482	0.630
	−0.321	0.140	0.020	−0.596	−0.047	−2.294	0.022

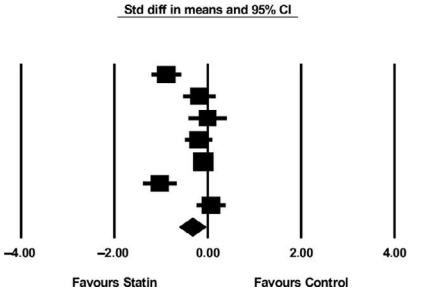


FIGURE 6 Forest plot for the post hoc analysis on the effect of type of statin therapy on plasma D-dimer concentrations with lipophilic statins above and hydrophilic statins below. Effect sizes were expressed as standardized mean difference (SMD) with its corresponding 95% confidence intervals (CIs) using Cohen's d as the summary statistic. A random-effects model was used for performance of the meta-analysis

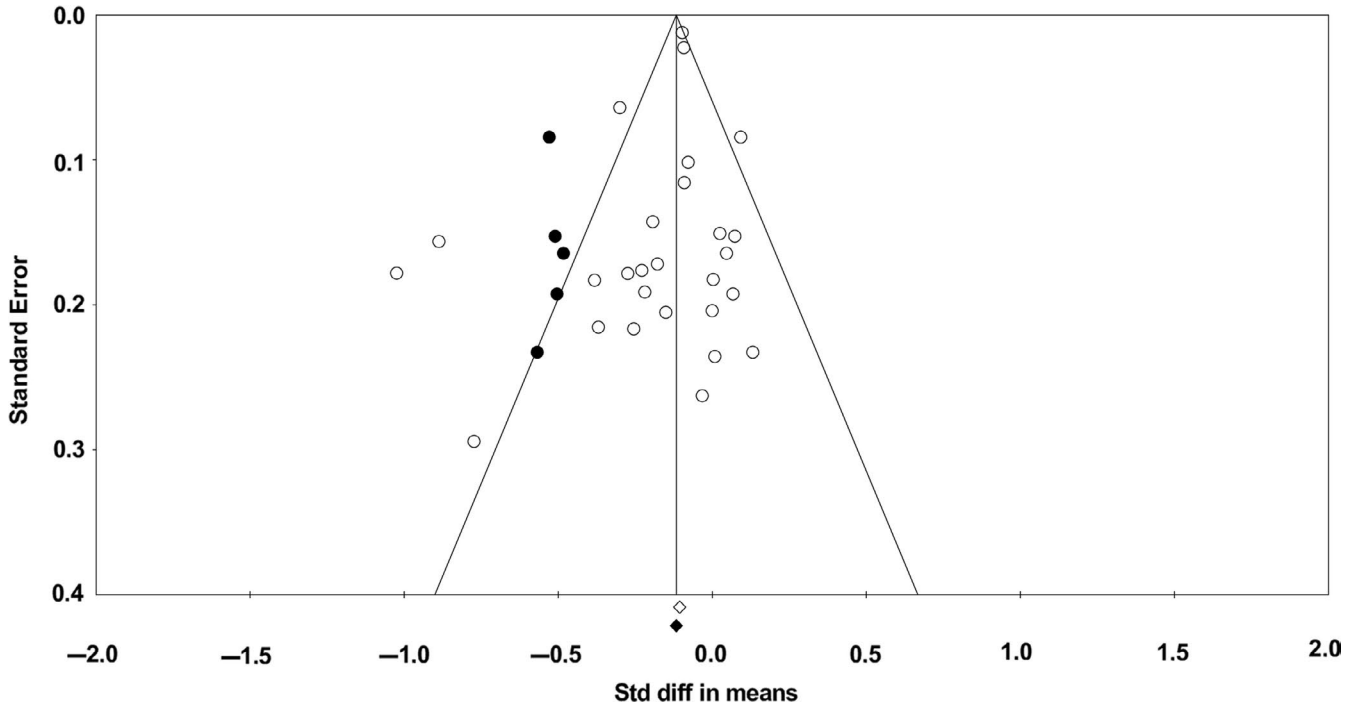


FIGURE 7 Funnel plot representing publication bias within literature analysed with Duval and Tweedie's trim-and-fill method about the effect of statin therapy on D-dimer levels. Observed studies are shown as open circles, and imputed studies are shown as filled circles

effect sizes.[25,64] Effect sizes should also be set in clinical perspective, incorporating that small effects could have large implications in clinical settings. In the article by Sahebkar et al therefore, the overall effect of statins on the plasma D-dimer levels could have been interpreted as a large effect (d = −0.988), but not as a reduction of D-dimer levels by

0.988 μg/mL (which would be an extremely large effect). Second, in the meta-analysis by Sahebkar et al we found inconsistencies in data extracted from the incorporated studies (Table S2). In seven of the nine studies, differences in mean (standard deviation [SD]) D-dimer levels were reported incorrectly in Table 1 of their meta-analysis.[12] For example, in both studies of Sommeijer et al and Walter et al, D-dimer values after treatment were reported as D-dimer changes.[26,31] Third, in our meta-analysis we explained essential assumptions with respect to the interpretation of the original data. In the meta-analysis by Sahebkar et al on the other side, it remains unclear how exactly means or SDs were estimated if not reported in the study manuscripts. Because of concerns on the validity of the reported D-dimer results, due to inconsistent calculation of D-dimer changes, results of sensitivity analyses and unstandardized D-dimer measurement, one could argue about inclusion of the studies of Dangas et al, Min et al and Undas et al.[65-67] In our meta-analysis, we excluded these three studies.

The results of our meta-analysis should of course also be interpreted with caution. In this meta-analysis, we did not only include randomized controlled trials, but also cohort and cross-sectional studies. In the two latter types of studies, we scored the risk of bias to be high and heterogeneity between individual studies will be higher. The meta-analysis was not limited to randomized controlled trials only, because we would then have ignored a large number of observational evidence.[68] It is however important to note that within the group of cross-sectional studies, there are some differences in the retrieved data. The study of Adams adjusted results of D-dimer levels in statin users and nonusers for the following potential confounding factors: age, sex, education, individual income, race, smoking status, current alcohol use, body mass index, diabetes status, hypertension, use of acetylsalicylic acid and hormone therapy use among women.[46] On the other hand, Walter et al matched users of atorvastatin with controls according to their total cholesterol levels and Kaba et al and Vidula et al did not adjust D-dimer levels for any confounding factors.[28,31,35] However, age and sex, two of the most influencing confounding factors, were not significantly different among statin users and nonusers in these studies. Also, duration of statin treatment was not assessed in these cross-sectional data. The described between-study heterogeneity is unlikely to have had a large impact on the results of our meta-analysis. In the subanalyses of the 6 controlled trials with low risk of patient selection and the 16 studies with low risk of limited patient applicability, change in D-dimer levels was not significantly different from the overall effect with all studies included. Also, a separate subanalysis only including the controlled trials did not differ from these results and resulted in lower D-dimer values after statin treatment. Moreover, the post hoc analyses on treatment duration and statin type did not show a difference. Another concern might be that the included studies were heterogeneous in the characteristics of study participants. Studies were performed in patients with proven cardiovascular disease, HIV infection, type 2 diabetes mellitus, lupus and COPD and in heart transplant patients. All these conditions could have influenced D-dimer levels. By running our meta-analysis with a random-effects model, we assumed the studies to be heterogeneous and our sensitivity analysis was robust. Furthermore, we could not fully exclude that publication bias has had an effect on the results of the meta-analysis. The adjusted effect size using the trim-and-fill method though was even larger than what we had observed, indicating that the effect size of reduction of D-dimer levels in statin users is more likely to be an underestimation rather than nonsignificant. Also, Begg's rank correlation and Egger's test were nonsignificant, indicating no publication bias and many missing studies (n = 422) would be needed and imputed in our meta-analysis to come to a nonsignificant effect.

In conclusion, in this meta-analysis use of statins was associated with a reduction of D-dimer levels, independent of treatment duration and type of statin used. This antithrombotic effect is part of the "pleiotropic" effects of statins and contributes to the benefits of statins on cardiovascular outcomes. The reduction of D-dimer levels in statin users may affect the performance of diagnostic algorithms on suspected VTE in this specific patient group, and prospective studies investigating the impact of statin use on these diagnostic algorithms are recommended.

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CONFLICT OF INTEREST

None of the authors reports a conflict of interest with regard to this manuscript.

AUTHOR CONTRIBUTIONS

SS-G, MK and TvG designed the study. SS-G and FM selected the articles and managed the study with support and input from all other authors. SS-G, JV, HB and LRA verified the data, which was analysed by LRA and interpreted by all other authors. SS-G wrote the first draft of the manuscript, which was reviewed, modified and approved by all other authors.

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