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Statins and secondary prevention of venous thromboembolism: pooled analysis of published observational cohort studies

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Abstract

Aims There have been suggestions that statins may have a potential role in secondary prevention of venous thromboembolism (VTE) [which includes deep vein thrombosis (DVT) and pulmonary embolism (PE)], but the evidence is inconsistent. We aimed to evaluate the association between statin use and risk of recurrent VTE.

Methods and Results We conducted a systematic review and meta-analysis of observational cohort studies. All relevant studies which reported associations between statin use and recurrent VTE outcomes were identified from MEDLINE, EMBASE, Web of Science, and manual search of bibliographies from inception to January 2017. Study specific relative risks (RRs) with 95% confidence intervals were aggregated using random effects models. Eight eligible studies comprising of 103,576 participants and 13,168 recurrent VTE outcomes were included in the pooled analysis. In pooled analysis of 7 studies, the RR for recurrent VTE was 0.73 (0.68-0.79) when comparing statin use with no use. There was no evidence of heterogeneity between contributing studies ($I^2=0\%$, 0 to 71%; $p=0.93$). The RRs for recurrent PE (three studies) and DVT (two studies) comparing statin use with no statin use were 0.75 (95% CI: 0.58 to 0.96) and 0.66 (95% CI: 0.60-0.71) respectively.

Conclusions Available evidence from observational cohort studies suggests a beneficial effect of statin use on VTE recurrence. Well-designed intervention studies are needed to corroborate these findings.

Keywords: statin; venous thromboembolism; venous thrombosis; pulmonary embolism; secondary prevention; systematic review; meta-analysis

Introduction

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, commonly called statins, are well established for the primary and secondary prevention of cardiovascular disease (CVD)¹⁻³, based on their lipid-lowering properties. Statins are also known to have pleiotropic effects that modulate coagulation and inflammation⁴. In recent years, there has been an emerging interest in the potential role of statins to reduce the incidence of VTE [which includes deep vein thrombosis (DVT) and pulmonary embolism (PE)]. Since the publication of the Heart and Estrogen/progestin Replacement Study (HERS), which reported an approximately 50 percent risk reduction in VTE in a nonrandomised comparison of statin versus nonstatin users⁵, and the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial which demonstrated that rosuvastatin significantly reduced the incidence of VTE⁶; several observational studies as well as randomised control trials (RCTs) have been published, but their results though suggestive of a protective effect have mostly been inconclusive. A number of reviews that have aggregated the existing data have also reported mixed results^{7, 8}. A recent comprehensive meta-analysis of 36 published studies has demonstrated a beneficial effect of statin use on VTE in both observational and intervention studies.⁹ Venous thromboembolism affects several millions of people globally and is an important cause of morbidity and mortality¹⁰. Patients with a first episode of VTE are at increased risk of further episodes. The recurrence of VTE is a major clinical problem and usually requires a more prolonged period of anticoagulation, in some cases indefinitely, thus adding to drug burden in these groups of patients. The role of statins in the secondary prevention of VTE is of emerging clinical interest. However, only a limited number of studies have explored the effect of statins on VTE recurrence and their results have been inconsistent^{11, 12}. Though anticoagulation is a very effective therapy for preventing VTE recurrence, balancing the risk of VTE recurrence with anticoagulant therapy is associated with about a 5-fold increase with major bleeding¹³. Since statins are safe, inexpensive, and do not increase bleeding risk, it will be of immense clinical benefit if they are demonstrated to have a role in preventing VTE recurrence. In this context, we aimed to clarify the uncertainties on the putative role of statins in the secondary prevention of VTE, by conducting a pooled analysis of available studies published so far on the topic.

Methods

We conducted this review using a predefined protocol and in accordance with PRISMA and MOOSE guidelines (**Supplementary Materials 1 and 2**). We searched MEDLINE, EMBASE and Web of Science electronic databases from inception up to January 25, 2017, using free and medical subject headings and combination of key words related to related to statins (e.g., *statin*, *hydroxymethylglutaryl-CoA reductase inhibitors*) and outcomes (e.g., *venous thromboembolism*, *deep vein thrombosis*, *pulmonary embolism*) in humans, without any language restriction. Reference lists of selected studies and relevant reviews identified on the topic were manually scanned for additional citations missed by the electronic search. Details of the search strategy, which was verified by a qualified Information Specialist, are presented in **Supplementary Material 3**. Observational cohort (prospective cohort, retrospective cohort, case-cohort, or nested case-control) studies or RCTs were eligible for inclusion if they assessed the association of any or current statin use with recurrent VTE, DVT, or PE outcomes in adults (≥ 18 years old) with prior VTE. Two reviewers independently abstracted data and performed quality assessments using a standardized predesigned data collection form. Venous thromboembolism outcomes were extracted as reported by the eligible studies. We assessed study quality using the nine-star Newcastle–Ottawa Scale (NOS)¹⁴ which is based on pre-defined criteria namely: selection (population representativeness), comparability (adjustment for confounders), and ascertainment of outcome. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflects the highest study quality. A score of ≥ 5 indicated adequate quality for inclusion in the review. The primary outcome of this analysis was recurrent VTE, which was reported by majority of studies.

Summary measures were presented as relative risks (RRs) with 95% confidence intervals (CIs). Due to the small number of VTE studies available for pooling, the summary RR was calculated by pooling study-specific estimates using the random effects Knapp-Hartung approach for small-sample adjustments.¹⁵ However, given that the Knapp-Hartung approach may overestimate the amount of uncertainty, particularly when dealing with 5 or fewer studies;¹⁶ the DerSimonian–Laird random effects model was used to pool studies of PE and DVT. Statistical heterogeneity across studies was

quantified using the Cochrane χ^2 statistic and the I^2 statistic¹⁷ To contextualise our results, we also calculated the number needed to treat (NNT) using the formula: $NNT = 1 / \text{absolute risk reduction (ARR)}$. All statistical tests were two-sided and used a significance level of $P < 0.05$ and Stata release 14 (StataCorp LP, College Station, TX, USA) software was used for all statistical analyses.

Results

Eight observational prospective cohort studies were found to be eligible^{11, 12, 18-22} (**Figure 1**). No RCT was identified, however one study was based on a post-hoc analysis of an extended follow-up of a RCT²⁰. One study was based on an abstract published in 2015, but the complete findings have not yet been published in a peer-reviewed journal.²³ Overall, we judged all of the included studies to be of adequate quality (quality score: 5-9). Seven studies reported on recurrent VTE (103,576 participants; 13,168 events), three on recurrent PE (75,285 participants; 4,703 events), and two on recurrent DVT (72,192 participants; 3,380 events). Two studies reported on all outcomes of recurrent VTE, PE, and DVT.^{18, 19} Except for one study with an average follow-up of 6-12 months, duration of follow-up ranged from 2.5 to 5.2 years. Five studies were based in Europe (Denmark, the Netherlands, and France), two in North America (USA in Canada), and one was conducted at 263 sites in 38 countries (**Table**). Comparing statin use with no statin use, there was a significant reduction in risk of recurrent VTE 0.73 (95% CI: 0.68 to 0.79) (**Figure 2**). There was no evidence of heterogeneity between the contributing studies ($I^2=0\%$, 0 to 71%; $p=0.93$). Two studies utilized participants from the Danish National Patient Registry. Though participants were recruited at different baseline years, there was a possibility of overlap of some participants^{18, 19}. Exclusion of any of these two studies one at a time from the meta-analysis had minimal effect on the pooled RR. On exclusion of the results based on the abstract, the pooled RR was 0.73 (95% CI: 0.67 to 0.80). The RRs for recurrent PE and DVT comparing statin use with no statin use were 0.75 (95% CI: 0.58 to 0.96) and 0.66 (95% CI: 0.60 to 0.71) respectively (**Figure 2**). The absolute risk reduction of recurrent VTE associated with statin use was 0.27% which translates into a NNT of 370 (95% CI: 313 to 476) to prevent one recurrent VTE.

Discussion

Though a limited number of studies have suggested a beneficial effect of statins on VTE recurrence, the results have mostly been mixed. Some studies have shown a protective effect, whereas others have reported null associations. By aggregating data from these available epidemiological observational cohort studies involving patients with prior VTE, we have shown a protective effect of statin use (27% relative risk reduction) in the secondary prevention of VTE (including PE and DVT). The results add to accumulating evidence that statins may have a potential role to play in both primary and secondary prevention of VTE.

Statins are known to have several vascular protective effects and which have been attributed to their anti-inflammatory and antithrombotic properties²⁴. The postulated mechanisms by which statins protect against VTE include downregulation of the blood coagulation cascade leading to reduced thrombin formation²⁵; inhibition of the coagulation cascade²⁶; and via their profibrinolytic and antiplatelet properties^{24,27}. Though our findings do not establish causality, they do underscore a potential role of statin therapy in the secondary prevention of VTE in addition to their established role in CVD prevention and beneficial effects on multiple disease conditions²⁸. Our absolute risk reduction of 0.27% as suggested by our meta-analysis translates to about 1,110 people that need to be treated to prevent one recurrent VTE in a year. However, this estimate assumes that the effect of statin use is constant over time and recurrent VTE events occur at a constant rate over time²⁹. Anticoagulant therapy is very effective at reducing VTE recurrence, but increases the risk of major haemorrhage, especially over long-term treatment. Anticoagulant therapy is only discontinued when the risk of bleeding and inconvenience of remaining on treatment far outweighs the risk of recurrent VTE. However, for most patients with a second VTE, lifelong treatment is recommended³⁰. Though the absolute risk reduction estimate does seem encouraging, statins compared with anticoagulant therapy have a good safety profile and do not cause bleeding. Moreover, our estimated absolute risk reduction was based on the assumption that recurrent VTE occurs at a constant rate over time. Secondary prevention of VTE may be another potential indication of statins; however, to echo a previous report by Gaertner et al.³¹, it is still too early to make any guideline recommendations based on the current

evidence. Well-designed intervention studies are now needed to corroborate this evidence and the benefits of statins also need to be balanced against the potential for harm.

To our knowledge, this is the first study to evaluate relevant studies that have assessed associations between statin use and VTE recurrence using a systematic meta-analytic approach. We were able to harmonize data from the limited studies to perform a quantitative analysis, which enhanced power, and therefore the ability to quantify more reliably the nature and magnitude of the association. We found no evidence of heterogeneity between contributing studies. Given the lack of relevant clinical trials published on this specific topic, our review was based on only observational evidence, which precluded the ability to make any causal inferences. Ideally, the assessment of the NNT should be made within a RCT. There were only a small number of studies available for pooling and there is a possibility that the precision of the summary estimates for PE and DVT may have been overestimated; given that the DerSimonian and Laird random effect model tends to produce narrow confidence intervals when there are small number of studies involved.¹⁶ Pooled analysis was based on variably adjusted data reported by the eligible studies, therefore prone to confounding by unmeasured factors. However, all studies adjusted for a comprehensive panel of confounding factors. Finally, we were unable to explore for the effects of publication bias given the limited number of studies. The findings should therefore be interpreted with caution given these limitations.

Conclusion

Available evidence supports an association between statin use and reduction in the risk of recurrent VTE. This review also highlights important gaps in the existing literature and the need for well-designed intervention studies to confirm the potential role of statins in the secondary prevention of VTE.

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Authors' contributions

S.K. K., S. S., and K. K. conceived and designed the study. S.K. K., S. S., and K. K. acquired data. S.K. K. analyzed and interpreted the data. S.K. K. drafted the manuscript. S.K. S.K. K., S. S., and K. K. critically revised the manuscript for important intellectual content. K. K. supervised the study. S.K. K. is the guarantor of this work, and as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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Disclosure of Conflict of interests

S. Seidu has received honoraria for speaking at meetings and serving on Advisory Boards for Novartis, Novo Nordisk, Janssen, MSD, Lilly and BI. K. Khunti has acted as a consultant and speaker for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen and Boehringer Ingelheim. He has received grants in support of investigator and investigator initiated trials from Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim and Merck Sharp & Dohme and Roche. K. Khunti has served on advisory boards for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen and Boehringer Ingelheim. S.K. Kunutsor has no conflict of interest.

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Figure Legend

Figure 1: PRISMA flow diagram

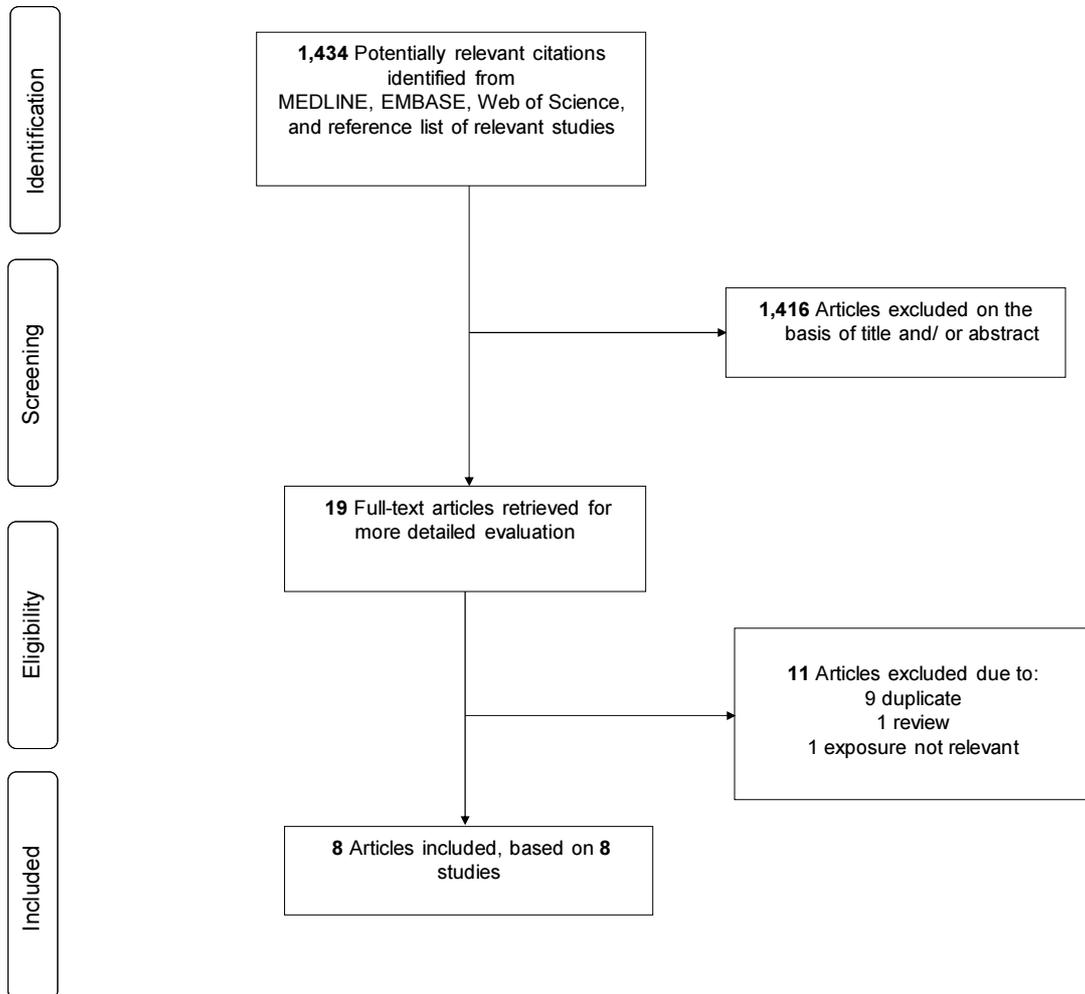
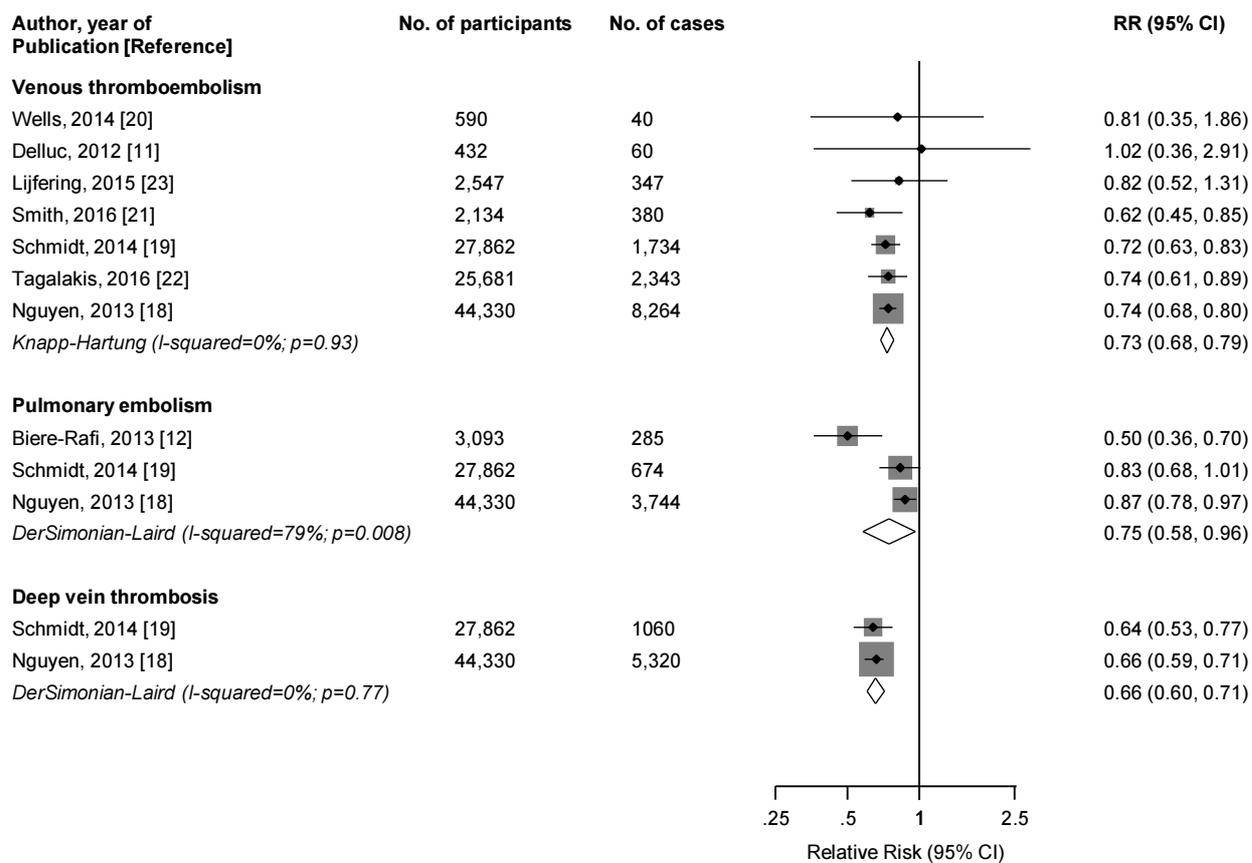


Figure 2: Association of statin use with risk of venous thromboembolism



CI, confidence interval (bars); RR, relative risk

Table. Characteristics of published observational cohort studies evaluating associations between statin use and venous thromboembolism

Lead author, publication year [References]	Name of study or source of participants	Location of study	Year(s) of baseline survey	Baseline mean age (age range), years	% male	Duration of follow-up (years)	Total no. of participants	No. of cases	Outcome	Covariates adjusted for	Study quality
Delluc, 2012 [11]	Brest University Hospital	France	2000-2006	65.5 (≥ 18)	40.3	2.5	432	60	VTE	Age, sex, BMI, site of thrombosis, lipid lowering drugs, aspirin use, clopidogrel use, and duration of anticoagulation use before inclusion in study	7
Biere-Rafi, 2013 [12]	PHARMO Record Linkage System	Netherlands	1998-2008	61.3 (NR)	45.0	4.2	3,093	285	PE	Gender, previous CVD events, and VKA therapy	7
Nguyen, 2013 [18]	Hospitals in Denmark	Denmark	1997-2009	62.5 (NR)	49.0	3.0	44,330	8,264	VTE, PE, and DVT	Age, gender, low-dose aspirin, clopidogrel, IHD, acute MI, atrial flutter/fibrillation, PVD, DM, malignancies, HRT, diuretics, glucose-lowering medication, ACE inhibitors/angiotensin II antagonists, NSAIDs, and antipsychotic medication	8
Schmidt, 2014 [19]	Danish National Patient Registry	Denmark	2004-2012	NR	50.6	3.0	27,862	1,734	VTE, PE, and DVT	Age, gender, year of index diagnosis, classic provoking factors, cardiovascular co-morbidities, Charlson co-morbidity index, concurrent use of antipsychotic medication and hormone therapy, and time-varying use of aspirin and anticoagulant drugs	8
Wells, 2014 [20]	EINSTEIN VTE program	38 countries	2007-2011	58.4 (NR)	57.3	6-12 months	590	40	VTE	Age, prior rivaroxaban or VKA treatment	5
Lijfering, 2015 [23]*	MEGA	Netherlands	NR	NR	NR	5.2	2,547	347	VTE	Age, sex, and other potential confounders	-
Smith, 2016 [21]	Group Health Cooperative	USA	2002-2010	63.3 (18-89)	42.6	3.4	2,134	380	VTE	Age, sex, race, BMI, idiopathic incident event and time-dependent cancers, smoking status, CVD, anticoagulation therapy, aspirin use, hospitalization, fracture	9
Tagalakis, 2016 [22]	Administrative database	Canada	1994-2004	NR (≥65)	39.0	3.0	25,681	2,343	VTE	Age, year of incident VTE, sex, incident VTE type, nature of incident VTE (unprovoked vs provoked), myocardial infarction, congestive heart disease, peripheral vascular disease, atrial fibrillation, ischaemic stroke, transient ischaemic attack, hypertension, chronic obstructive pulmonary disease, DM, liver disease (including liver cirrhosis), hypothyroidism, hyperthyroidism, chronic renal disease, nephritis syndrome, inflammatory bowel disease, and previous use of statins and anticoagulants.	7

ACE, angiotensin converting enzyme; BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; DVT, deep vein thrombosis; HRT, hormone replacement therapy; IHD, ischaemic heart disease; MI, myocardial infarction; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; PE, pulmonary embolism; PVD, peripheral vascular disease; VKA, vitamin K antagonists; VTE, venous thromboembolism

*, Based on a published abstract.