Statin use and the prevention of venous thromboembolism: a meta-analysis

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SUMMARY

Aims: Statins are thought to have antithrombotic properties and may attenuate patients’ odds of developing venous thromboembolism (VTE), but clinical studies have yielded variable estimates of this effect. The aim was to conduct a meta-analysis to evaluate the effect of statin use on development of VTE. Methods: Randomised controlled trials (RCTs) and observational studies evaluating the effects of statins on the incidence of VTE were selected from MEDLINE (1996 to August 2009), Cochrane CENTRAL (second quarter, 2009), Cochrane Database of Systematic Reviews (second quarter, 2009) and a manual review of references. While no further restrictions were placed on RCTs, observational studies were only included if they reported adjusted effect sizes using appropriate methods. Development of deep vein thrombosis (DVT), pulmonary embolism (PE) and any VTE from RCTs and observational studies were pooled using traditional meta analytic techniques with a random-effects model. Results: Ten studies were identified and eligible for meta-analysis. Upon meta-analysis, statin use was associated with a statistically significant reduction in the odds of developing VTE (AOR 0.68, 95% CI 0.54–0.86), DVT (AOR 0.59, 95% CI 0.43–0.82) and PE (AOR 0.70, 95% CI 0.53–0.94). Discussion: Statin use is associated with significantly reduced odds of developing VTE, DVT or PE by 32%, 41% and 30% respectively. Our meta-analysis included one RCT, JUPITER, which alone provided statistically significant reduction in the odds of developing VTE and DVT (43% and 55% respectively), and a nonsignificant reduction on PE. Conclusion: Currently available evidence suggests that statins can reduce patients’ odds of developing VTE.

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs annually in about 1 in 1000 people in the United States, with two-thirds of cases being DVT, and the remaining third PE (1). Venous and arterial thromboses have largely been considered separate diseases (2), but recent evidence has suggested a link between them (2,3). Both states share common risk factors such as obesity, smoking and type 2 diabetes (2). Epidemiological evidence suggests that prior VTE increases the risk of atherosclerosis and also the converse, that atherosclerosis is a risk factor for VTE (2).

Statin use is associated with significantly reduced odds of developing VTE, DVT or PE by 32%, 41% and 30% respectively. Our meta-analysis included one RCT, JUPITER, which alone provided statistically significant reduction in the odds of developing VTE and DVT (43% and 55% respectively), and a nonsignificant reduction on PE. Conclusion: Currently available evidence suggests that statins can reduce patients’ odds of developing VTE.

Message for the Clinic

This meta-analysis describes the effect of statin use on the development of VTE, DVT and PE. Statin use is associated with significantly reduced odds of developing VTE, DVT or PE by 32%, 41% and 30% respectively.
In order to reconcile the conflicting results in the existing medical literature, we aimed to conduct a meta-analysis to describe and better understand the effect of statin use on the development of VTE.

**Methods**

**Study selection**

A literature search of MEDLINE (1996 to August 2009), Cochrane CENTRAL (second quarter, 2009) and the Cochrane Database of Systematic Reviews was conducted using search terms for VTE (‘venous thromb*’, ‘VTE’, ‘deep vein thrombosis’, ‘DVT’, ‘pulmonary embolism’), combined with terms for statins (‘statin’, ‘hmg’, ‘atorvastatin’, ‘simvastatin’, ‘statins’, ‘lovastatin’, ‘cerivastatin’, ‘pravastatin’, ‘fluvastatin’, ‘pitavastatin’). Search results were limited to human studies without language restriction. In addition, a manual reference search of included citations was performed to identify any additional relevant studies. Studies were eligible for inclusion in the meta-analysis if they were (i) randomised controlled trials (RCTs) or observational studies; and (ii) evaluated the effects of statin therapy on the incidence of VTE. While no further restrictions were placed on RCTs, observational studies were only included if they reported an adjusted estimate of effect using appropriate methods, including multivariate regression or covariate matching.

**Data abstraction**

Data were independently abstracted by two investigators with the use of a standardised data abstraction form. Disagreements were resolved by discussion or by a third investigator. The following information was sought from the studies: first author, year of publication, study design (RCT, prospective cohort, retrospective cohort, case–control), information to determine adequate control of potential confounding (randomisation, multiple regression, matching, by exclusion), confounders controlled for, funding sources, description of study population, exclusion criteria used, end-points reported (VTE, DVT, PE), definitions of end-points reported, effect measure reported, duration of follow-up and statin use, baseline characteristics of the population studied [sample size, age, gender, diabetes, cancer, atherosclerotic disease which included myocardial infarction, peripheral vascular disease and cerebrovascular accident, recent surgery, fracture, prior VTE, heart failure, hormone replacement therapy (HRT), recent pregnancy, aspirin use, immobilisation, chronic obstructive pulmonary disease, smoking], and results reported along with 95% confidence intervals (95% CIs).

**Quality rating**

Quality rating of studies was performed by two investigators using methodology recommended by the US Preventative Services Task Force (19). Specifically, hierarchy of study design, sample size, magnitude of effect size, and appropriateness of methods to control for confounding were considered. Studies were then given an overall ranking of ‘good’, ‘fair’ or ‘poor’.

**Statistical analysis**

The estimated adjusted effect [adjusted odds ratio (AOR) or adjusted hazards ratio] and associated 95% CIs for the development of VTE, DVT and PE were meta-analysed using a DerSimonian-Laird random-effects model, whereby studies are weighted in the meta-analysis based upon the inverse of the variance and adjusting for extent of variation among studies (20). Summary effect sizes with accompanying 95% CIs were calculated for the three outcomes. In one analysis, we pooled all available studies together; in a second analysis, we pooled only observational studies.

Statistical heterogeneity between individual studies was determined using the $I^2$ statistic, which provides the degree of heterogeneity not attributable to chance and ranges from 0% to 100%. Values of 25%, 50% and 75% represent low, moderate and high levels of statistical heterogeneity respectively. Publication bias was evaluated using visual inspection of funnel plots and Egger’s weighted regression statistics. Statistical analysis was performed using StatsDirect statistical software, version 2.7.6. A p-value of $< 0.05$ was considered representative of statistical significance for all analyses. Sensitivity analysis was performed excluding studies which were rated ‘poor’ in quality.

**Results**

Upon conducting the literature search, 49 unique citations were identified, 47 from the database search and two from manual reference searching. Thirty-six citations were excluded upon title and abstract review (10 were not clinical studies, 24 did not evaluate statins and two did not report useable end-points for meta-analysis), leaving 13 citations for full-text review. One of these was excluded because it was not a clinical study (21) and another was excluded because an adjusted effect size was not reported (22). Eleven publications were ultimately included, two of which reported on the same population (8,9), leaving only 10 studies for quantitative synthesis (Figure 1).
Study characteristics
Ten studies (9–18), including one RCT (18) and nine observational studies (9–17), were included. In total, the meta-analysis evaluated a total of 971,307 unique patients. Among the observational studies, there were six case–control (10–12,14–16), two retrospective cohort studies (15,17) and one prospective cohort study (9) (Table 1). Of the 10 studies, nine \((n = 845,445)\) were included in the VTE analysis (9–16,18), five \((n = 234,730)\) in the DVT analysis (10,11,14,17,18) and four \((n = 108,868)\) in the PE analysis (10,11,14,18). Among cohort studies and the one RCT (9,15,17,18), the control rate of VTE ranged from 0.21 to 1.09 events per 100 person-years.

Quantitative data synthesis
Upon meta-analysis, statin use was associated with a statistically significant reduction in the odds of developing VTE (AOR 0.68, 95% CI 0.54–0.86). Statistical heterogeneity was observed to be high between studies included in this analysis \((I^2 = 81.7\%)\), likely due to the varying magnitude of effects as all but two trials showed similar directions of effect. A low likelihood of publication bias was suggested by the funnel plot or Egger’s weighted regression statistic. Our results were consistent when only the observational studies were meta analysed, with a statistically significant reduction in the odds of developing VTE by 31% (Table 2, Figure 2).

Similar results were seen when meta analysing studies reporting the DVT end-point. Statin use was associated with a statistically significant reduction in the odds of developing DVT (AOR 0.59, 95% CI 0.43–0.82). A high degree of heterogeneity \((I^2 = 88.9\%)\) was detected, likely due to the varying magnitude of effects as all trials showed similar directions of effect. A low likelihood of publication bias was suggested by the funnel plot or Egger’s weighted regression statistic. A significant 38% reduction (95% CI 12–56%) in the odds of developing DVT was also found upon exclusion of the RCT from the analysis.

Statin use was associated with a statistically significant reduction in the odds of developing PE upon meta-analysis (AOR 0.70, 95% CI 0.53–0.94). A high degree of heterogeneity \((I^2 = 77.4\%)\) was present, though all but one trial showed a similar direction of effect. A low likelihood of publication bias was suggested by the funnel plot or Egger’s weighted regression statistic. When excluding the one RCT from the analysis, results remained similar to the combined
Table 1 Characteristics of studies which evaluated the effect of statin use on VTE

| Study, n | Type | Population | Exclusion criteria | Baseline lipid parameters | Variables adjusted in study results | Quality rating* |
|----------|------|------------|--------------------|---------------------------|--------------------------------------|----------------|
| Glynn et al. (4,18), n = 17,802 | Randomised controlled trial | Male subjects over age 50 years and female subjects over age 60 years, no history of cardiovascular disease, LDL-C less than 130 mg/dl, high-sensitivity C-reactive protein level 2.0 mg/l or more | Use of lipid-lowering therapy within 6 weeks before screening, use of HRT, cancer, DM and uncontrolled hypertension | Median values (Statin; Control, mg/dl) TC: 186; 185 LDL-C: 108; 108 HDL-C: 49; 49 TG: 118; 118 | None | Good |
| Ramcharan, et al. (10), n = 10,452 | Case–control | Cases were patients aged 18–70 years, with first episode of DVT or PE, from six anticoagulation clinics in the Netherlands between March 1999 and September 2004 Controls were partners of patients or obtained via random-digit-dialling method, aged 18–70 years from the same geographical area and frequency matched on age and gender | Severe psychiatric disease, lack of knowledge of Dutch, patients treated for VTE but not diagnosed and lack of information on medication use | NR | Regression model adjusted for BMI, age, gender, aspirin use, antiplatelet use, vitamin K antagonist use, atherosclerotic disease | Fair |
| Sørenson et al. (11), n = 64,064 | Case–control | All patients were in medical databases of patients living continuously since 1977 in the counties of North Jutland and Aarhus, Denmark Cases were patients hospitalised for DVT or PE Controls were alive at the diagnosis date of the corresponding case, without a hospital admission or outpatient VTE diagnosis | Outpatient diagnosis of patients without subsequent inpatient diagnosis, history of surgery, fractures, major traumas, pregnancy | NR | Regression model adjusted for BMI, age, gender, aspirin use, HRT use, anti-psychotic medication use, pregnancy, surgery, fractures, trauma, cancer, DM, atherosclerotic disease, heart failure | Fair |
| Lacut et al. (12), n = 1354 | Case–control | All patients were aged over 18 years hospitalised between May 2000 and December 2004 at Brent University Hospital Cases had objectively confirmed symptomatic VTE Controls were hospitalised patients matched by age and gender | Surgery, plaster cast immobilisation, pregnancy, or delivery in past 3 months, active cancer, previous documented VTE or lifelong anticoagulant therapy | NR | Regression model adjusted for BMI, age, gender, aspirin use, atherothrombotic disease, chronic pulmonary disease and family history of VTE | Fair |
| Study, n | Type | Population | Exclusion criteria | Baseline lipid parameters | Variables adjusted in study results | Quality rating* |
|----------|------|------------|-------------------|---------------------------|-------------------------------------|----------------|
| Smeeh et al. (13), n = 729,529 | Retrospective cohort | Patients aged 40–80 years being seen between January 1995 and December 2006 in a general practice contributing to The Health Improvement Network database | NR | NR | Propensity score matching of controls on 38 variables, Regression model adjusted for age, gender, propensity score, index date, DM, cerebrovascular disease, CHD, peripheral vascular disease, other atheroma, atrial fibrillation, heart failure, hyperlipidaemia, hypertension, other circulatory disease, cancer, dementia, medication use (aspirin, nitrates, fibrates, beta blockers, calcium channel blockers, potassium channel activators, diuretics, positive inotropes, anticoagulants, antihypertensives or other cardiovascular drugs) | Fair |
| Huerta et al. (14), n = 16,550 | Case–control | Patients aged 20–79 years followed by a family physician enrolled in the General Practice Research Database (GPRD) in the United Kingdom, for at least 2 years starting in January 1994. Cases were those with recorded diagnosis of DVT or PE and received anticoagulant therapy. Controls randomly sampled and matched by age, gender and calendar year. | Patients with a history of DVT or PE, thrombophlebitis and upper extremity VTE or no anticoagulant prescription | NR | Regression model adjusted for BMI, age, gender, warfarin use, smoking, cancer, fractures in the last month, surgery in the last 6 months and visits to the family physician in the last year | Fair |
| Doggen et al. (15), n = 2427 | Case–control | Cases were postmenopausal women aged 30–89 years with first VTE from 1 January 1995 to 31 December 2000. Controls were matched on age, calendar year and treated hypertension status | NR | NR | Regression model adjusted for age, and vascular disease (history of MI, angina, stroke, TIA or claudication) | Poor> |
Table 1 (Continued)

| Study, n | Type                  | Population                                                                 | Exclusion criteria                                                                 | Baseline lipid parameters | Variables adjusted in study results                                                                 | Quality rating* |
|----------|----------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------|-----------------|
| Herrington et al. (9) and Yang and Kao (22), n = 2763 | Prospective cohort | Postmenopausal women in the HERS randomised controlled trial (under age 79 years with intact uterus and CHD evidenced by prior MI, CABG surgery, mechanical revascularisation or angiographic evidence of at least 50% occlusion) | Qualifying CHD event within 6 months, postmenopausal HRT within 3 months, HRT contraindicated | Mean values (Statin; No Statin, mg/dl) TC: 221; 234 LDL-C: 135; 151 HDL-C: 51; 50 TG: 160; 165 | Regression model adjusted for race, DM, hypertension, creatinine clearance less than 40 ml/min, LDL-C, HDL-C, prior MI and heart failure | Fair |
| Yang et al. (16), n = 504 | Case–control | All patients were aged 40–79 years from the GPRD database from January 1991 to December 1999 Cases were those hospitalised with a first-time diagnosis of idiopathic VTE Controls were matched on gender, practice, calendar year and years of history in GPRD | History of VTE, cerebrospinal disease, coronary or peripheral artery disease, heart failure, cancer, coagulopathies, vasculitis, chronic renal diseases, complicated HTN, DM, alcohol/drug abuse, epilepsy and ≥ 80 years of age | NR | Regression model adjusted for age, calendar year and gender | Poor |
| Ray et al. (17), n = 125,862 | Retrospective cohort | Patients aged at least 65 years enrolled with the Ontario Health Insurance Plan | History of angina, MI, coronary revascularisation, stroke, carotid endarterectomy, peripheral vascular disease, peripheral artery revascularisation, diagnosis of cancer, DVT or PE within 36 months, or warfarin within 12 months prior to study | NR | Regression model adjusted for age, gender, aspirin use, warfarin use, oestrogen use, recently diagnosed cancer, prior hospitalisation | Fair |

*Studies rated using criteria recommended by the US Preventative Services Task Force. BMI, body mass index; CABG, coronary artery bypass graft; CHD, coronary heart disease; DM, diabetes mellitus; DVT, deep vein thrombosis; HDL-C, high-density lipoprotein cholesterol; HERS, Heart and Estrogen/progestin Replacement Study; HMO, health maintenance organisation; HRT, hormone replacement therapy; GPRD, General Practice Research Database; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NR, not reported; PE, pulmonary embolism; TC, total cholesterol; TG, triglycerides; TIA, transient ischaemic attack.
Table 2 Results of meta analysis of studies which evaluated the effect of statin use on VTE, DVT or PE

|                  | n     | No. of studies | AOR (95% CI)       | $i^2$ (%) | Excluding studies with ‘poor’ rating* |
|------------------|-------|----------------|--------------------|-----------|-----------------------------------|
| VTE              |       |                |                    |           |                                   |
| All studies      | 845,445 | 9              | 0.68 (0.54–0.86)   | 82        | 0.67 (0.52–0.87)                   |
| RCT              | 17,802 | 1              | 0.57 (0.37–0.86)   | NA        | 0.57 (0.37–0.86)                   |
| Observational    | 827,643 | 8              | 0.69 (0.54–0.89)   | 83        | 0.68 (0.52–0.91)                   |
| DVT              |       |                |                    |           |                                   |
| All studies      | 234,730 | 5              | 0.59 (0.43–0.82)   | 89        | 0.59 (0.43–0.82)                   |
| RCT              | 17,802 | 1              | 0.45 (0.25–0.79)   | NA        | 0.45 (0.25–0.79)                   |
| Observational    | 216,928 | 4              | 0.62 (0.44–0.88)   | 91        | 0.62 (0.44–0.88)                   |
| PE               |       |                |                    |           |                                   |
| All studies      | 108,868 | 4              | 0.70 (0.53–0.94)   | 67        | 0.70 (0.53–0.94)                   |
| RCT              | 17,802 | 1              | 0.77 (0.41–1.45)   | NA        | 0.77 (0.41–1.45)                   |
| Observational    | 91,066 | 3              | 0.70 (0.50–0.98)   | 77        | 0.70 (0.50–0.98)                   |

*Studies rated using criteria recommended by the US Preventative Services Task Force. AOR, adjusted odds ratio; DVT, deep vein thrombosis; NA, not applicable; PE, pulmonary embolism; RCT, randomised controlled trial; VTE, venous thromboembolism.

Figure 2 Results of meta-analysis of studies which evaluated the effect of statin use on venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE)
analysis, showing a 30% (95% CI 2–50%) reduction in PE with statin use compared with no use.

Results were not significantly altered for any endpoints upon sensitivity analysis excluding ‘poor’ quality studies.

Discussion

Our meta-analysis suggests that statin use is associated with significantly reduced odds of developing VTE, DVT or PE by 32%, 41% and 30% respectively. When evaluating observational studies alone, results were similar and remained statistically significant. Our meta-analysis included one RCT, JUPITER, which alone provided statistically significant reduction in the odds of developing VTE and DVT (43% and 55% reduction respectively), and a nonsignificant reduction on PE.

As the only RCT, the JUPITER trial published by Glynn et al. provides the strongest evidence on the effect of statins on VTE development, specifically with rosuvastatin. JUPITER enrolled generally healthy patients without inherent risk of VTE (18). Consequently, control rates for VTE, DVT and PE of 0.32, 0.20 and 0.12 events per 100-person years, respectively, were observed (18). It is possible that the nonsignificant effect seen on PE is due to a low control group event rate, providing an underpowered analysis. Our meta-analysis, upon analysing the totality of study evidence, was able to demonstrate a statistically significant effect of statins of PE.

In the HERS trial, the rate of VTE development in the control group was 0.61 per 100-person years, a value much higher than that of the JUPITER trial (9). Patients in the HERS trial likely had greater risk of developing VTE, due to their age and postmenopausal status requiring HRT (23). However, the benefits provided by statins were similar in both populations (66% reduction in the HERS trial and 43% reduction in JUPITER), suggesting that the reduction in the odds of developing VTE may be independent of baseline risk.

Factors which influence endothelial function, alterations in blood flow and hypercoagulability of blood contribute to the development of VTE (24). Thrombus formation can be initiated by two platelet activation mechanisms: (i) disrupted endothelial tissue may activate platelets through exposure of subendothelial matrix and collagen accumulation or (ii) through endothelial tissue factor activation (25). Tissue factor also plays a role in the coagulation cascade, initiating thrombin generation and fibrin formation (25). Statins may inhibit the expression of tissue factor, thereby preventing the downstream effects on platelet activation and on the coagulation cascade (7). Thus, it is not unreasonable to hypothesise that they can reduce VTE incidence.

Development of VTE has also been linked to certain clinical conditions, which may be attenuated by statin use. Observational evidence shows an association between VTE and metabolic syndrome (26), atherosclerosis (27) and prior cardiovascular events (11). Statins have previously been shown to positively attenuate these conditions, and therefore, this may also serve as a potential mechanism by which statins reduce the risk of VTE.

Currently it is unknown whether VTE reduction is a class effect of statins. One study included in our meta-analysis suggested that simvastatin, but not pravastatin, provided benefit (15). However, a larger study by Ramcharan et al. came to a conflicting conclusion. In this study, pravastatin trended towards having a greater odds reduction in VTE than simvastatin (10). Moreover, it is also unknown if a statin’s benefit on VTE is dose or potency-related. We were unable to evaluate these hypotheses in our meta-analysis due to a paucity of studies reporting their results by individual statin and/or statin dose.

There are some additional limitations to our meta-analysis that should be noted. First, although we found that statin use is associated with decreased odds of developing VTE, DVT and PE, most of the data were derived from observational studies, which often suffer threats to their internal validity. Larger randomised trials, evaluating these outcomes as primary end-points should be conducted to confirm JUPITER’s and our conclusions. Future trials should also attempt to determine whether this is a class effect seen with all statins and whether the effect is dose-dependent. Finally, in all analyses, a moderate to high degree of statistical heterogeneity was observed. One potential explanation for the observed heterogeneity is the varying degrees of baseline VTE risk among included studies. However, in most cases, studies showed similar directions of statin effect (benefit), with differences occurring instead in the magnitude of the effect.

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References

1 White RH. The epidemiology of venous thromboembolism. Circulation 2003; 107(Suppl. 1): 14–8.
