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REVIEW

Statins and prevention of venous thromboembolism: Myth or reality?

Statines et prévention de la maladie veineuse thromboembolique : mythe ou réalité ?

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Review

Summary The pleiotropic effects of statins, beyond their cholesterol-lowering properties, are much debated. In primary prevention, several observational cohort and case-control studies appear to show that statins reduce the incidence of venous thromboembolism by about 30%. In a single randomized placebo-controlled clinical trial (JUPITER), which included 17,000 patients, rosuvastatin 20 mg/day reduced the risk of venous thromboembolism by 43%. However, these patients were at low risk of venous thromboembolism, and the frequency of the event was, in principle, low. In secondary prevention, several observational studies and post-hoc analyses of randomized clinical trials have suggested that statins may prevent recurrence of venous thromboembolism. However, none of these studies had enough scientific weight to form the basis of a recommendation to use statins for secondary prevention. The putative preventive effect of statins appears to be independent of plasma cholesterol concentration and could be a pharmacological property of the statin class, although a dose-effect relationship has not been demonstrated. The mechanism through which statins might prevent venous thrombosis is thought to involve their anti-inflammatory and antioxidant effects or perhaps a more specific action, by blocking the degradation of antithrombotic proteins. A mechanism involving the action of statins on interactions between risk factors for atherosclerosis and venous

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; OR, odds ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

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thromboembolism is supported by some studies, but not all. In the absence of firm evidence, statins cannot currently be recommended for primary or secondary prevention of venous thromboembolism.

MOTS CLÉS
Maladie thromboembolique veineuse ;
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Résumé Au-delà de la réduction du taux de cholestérol plasmatique, les effets pléiotropes des statines sont discutés. En prévention primaire, plusieurs études observationnelles de type registres ou études cas-témoins semblent montrer un effet réducteur des statines d'environ 30 % sur la fréquence de la maladie veineuse thromboembolique. Un seul essai clinique contrôlé et randomisé (JUPITER), comparant la rosuvastatine 20 mg/jour au placebo et ayant inclus 17 000 patients, a montré une réduction du risque de maladie thromboembolique veineuse de 43 % dans le groupe statine. Il s'agissait, cependant, de patients à faible risque de maladie thromboembolique veineuse chez lesquels la fréquence de l'évènement était a priori basse. En prévention secondaire, quelques études observationnelles ou analyses post-hoc d'essais cliniques randomisés suggèrent un possible effet préventif des statines sur la récidive de maladie thromboembolique veineuse. Cependant, aucune de ces études n'avait le poids scientifique permettant de recommander l'utilisation des statines en prévention secondaire. L'effet préventif possible des statines paraît indépendant des taux plasmatiques du cholestérol et pourrait être relié à la classe pharmacologique elle-même sans qu'une relation dose-effet puisse être construite. Le mécanisme préventif des statines sur le thrombus veineux ferait intervenir les effets anti-inflammatoires et anti-oxydants des statines, voire une action plus spécifique bloquant la dégradation des protéines anti-thrombotiques. Une action des statines via des liens entre les facteurs de risque de l'athérosclérose et la maladie thromboembolique veineuse est discutée. Aujourd'hui, en l'absence de preuves fermement établies, les statines ne peuvent être recommandées en prévention primaire ou secondaire de la maladie thromboembolique veineuse.

Background

Statins reduce the risk of onset or recurrence of conditions and events caused by atheroma, such as coronary heart disease, angina, myocardial infarction, peripheral artery disease and stroke [1,2]. This effect is observed regardless of initial cholesterol concentration in patients at both high and low risk of cardiovascular disease [3–5]. In addition to their cholesterol-lowering effect, the pleiotropic effects of statins, based mainly on their anti-inflammatory and antioxidant properties, have been debated ever since they came into use. A preventive effect was thus postulated in heart failure, certain cancers, osteoporosis and dementia. A number of observational studies published in the 2000s suggested that statins might also have a preventive effect against venous thromboembolism (VTE) [6–11]. More recently, the randomized placebo-controlled trial JUPITER provided more tangible evidence of the possible efficacy of statins in the primary prevention of VTE [12]. These studies employed very different designs and methodologies, and the conclusions of meta-analyses have been inconsistent [13–17]. High quality evidence for the value of statins in secondary prevention is lacking, as the current data were obtained from observational studies or post-hoc analyses of clinical trials [18–21]. We will consider in turn the results of the main studies published on the use of statins in primary and secondary prevention of VTE, before addressing mechanisms that could explain their possible efficacy, a subject that remains a source of debate.

Statins and primary prevention of VTE

Not long after statins were first marketed, it was hypothesized that they might have pharmacological properties beyond simply lowering plasma cholesterol concentrations. The results of observational cohort and case-control studies published in the 2000s hinted at a possible preventive effect against VTE (Table 1). This aspect of the pharmacological properties of statins was first studied in postmenopausal women, a population at increased risk of both arterial and venous thromboembolic events. The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized clinical trial designed to study the effects of oestrogen and progesterone supplementation on cardiovascular morbidity and mortality, conducted in 2763 postmenopausal women with coronary heart disease [8]. The authors later compared the incidence of VTE events in the statin users

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Table 1 The main studies that measured the influence of statins on the incidence of venous thromboembolism.

Study	Design	OR [95% CI]	Level of evidence[a]
HERS; Grady et al., 2000 [8]	RCT; post-hoc analysis in 2763 postmenopausal women with CHD	0.50 [0.2—0.9]	Low
GHC; Doggen et al., 2004 [7]	Case-control in postmenopausal women (465 cases, 1962 controls)	0.84 [0.51—1.37]	Low
Ontario Residents Cohort Study; Ray et al., 2001 [11]	Retrospective cohort study in 125,862 men and women aged > 65 years; 77,993 statin users	Total 0.78 [0.69—0.87]; women 0.72 [0.63—0.82]; men 0.97 [0.78—1.22]	Low
EDITH; Lacut et al., 2004 [9]	Case-control (377 patients/group); hospital-based	0.42 [0.23—0.76]	Low
MEGA; Ramcharan et al., 2009 [10]	Case-control (4538 cases, 5914 controls); population-based	0.55 [0.46—0.67]	Low
Olmsted County; Ashrani et al., 2015 [6]	Case-control (1340 cases, 1538 controls)	0.73 [0.55—0.96]	Low
JUPITER; Glynn et al., 2009 [12]	RCT (17,804 patients); rosuvastatin 20 mg/day versus placebo	0.57 [0.37—0.86]	High

CHD: cardiovascular heart disease; CI: confidence interval; HERS: Heart and Estrogen/progestin Replacement Study; GHC: Group Health Cooperative; MEGA: Multiple Environmental and Genetic Assessment of risk factors for venous thromboembolism; OR: odds ratio (representing the risk of venous thromboembolism occurring in statin non-users); RCT: randomized controlled trial.
[a] Levels of evidence are based on the recommendations of the French National Authority for Health (HAS) [33].

included in the trial with that observed in the non-users. Statin use reduced the frequency of VTE events by 50% (relative hazard 0.5, 95% confidence interval [CI] 0.2—0.9). However, as this was a post-hoc analysis, it only provided low-level evidence. A case-control study was conducted by the health insurer Group Health Cooperative in Washington State, USA, between January 1995 and December 2000, in postmenopausal women aged between 30 and 89 years [7]. A group of 465 women who had a first VTE during the study period was matched with 1962 controls. At the time of their inclusion in the study, 4.5% of the cases and 5.6% of the controls were using a statin, mainly simvastatin or pravastatin. In this study, statin use was associated with a 16% reduction in the risk of VTE (odds ratio [OR]: 0.84, 95% CI: 0.51—1.37). This reduction was unaffected by adjustment for hormone replacement therapy use, body weight or the presence of diabetes.

Using data from Ontario provincial healthcare administrative databases, Ray et al. conducted a retrospective population-based study in Canada to determine the influence of statin use on the incidence of VTE [11]. The cohort consisted of 125,862 men and women aged > 65 years with neither cancer nor cardiovascular disease. The incidence of VTE in a group of 77,993 statin users was compared with that of a group of 11,891 patients prescribed a non-statin lipid-lowering drug, and 35,978 patients for whom thyroid hormone replacement had been prescribed. The authors postulated that patients with hypothyroidism were not at increased risk of VTE, and could therefore constitute a control group. Compared with the control group, the VTE risk was 22% lower among statin users (adjusted hazard ratio [HR]: 0.78, 95% CI: 0.69—0.87). The reduction was significant when only women were considered (HR: 0.72, 95% CI: 0.63—0.82), but not in men (HR: 0.97, 95% CI: 0.78—1.22). No risk reduction was observed in patients receiving non-statin lipid-lowering therapy (HR: 0.97, 95% CI: 0.79—1.18). Despite the large number of patients included in this study, it had certain limitations: its retrospective design, the failure to discriminate between the various statins available on the market at that time, and the potential confounding role of hormone replacement therapy among the women. Furthermore, the characteristics of these patients' lipid abnormalities were unknown.

Lacut et al. evaluated the environmental and genetic risk factors for VTE in the case-control EDITH study, conducted in Brest, France [9]. The authors analysed the role of statins in 377 patients hospitalized for pulmonary embolism and/or deep vein thrombosis, and the same number of controls hospitalized in cardiology or internal medicine at the same hospital. The cases and controls were matched for VTE risk factors. The higher frequency of statin use in the control group (9.5% of patients) compared with the VTE group (5%) equated to a risk reduction of 58% (OR: 0.42, 95% CI: 0.23—0.76; $P = 0.002$). This reduction was not observed in fibrate users (OR: 1.38, 95% CI: 0.76—2.52; $P = 0.26$). The risk reduction was at the limit of significance for aspirin (OR: 0.66, 95% CI: 0.42—1.05; $P = 0.06$), and was non-significant for thienopyridine users (OR: 1.07, 95% CI: 0.48—2.41; $P = 0.85$). After adjustment for aspirin use or atherosclerotic disease, statins retained a protective effect against VTE, suggesting that the effect is independent of these confounding factors. However, because this was a non-interventional case-control study, it only provides low-level evidence.

The MEGA (Multiple Environmental and Genetic Assessment of risk factors for VTE) study employed a population-based case-control study design [10]. This observational study, conducted at six hospitals in the Netherlands between 1999 and 2004, measured the influence of various drug regimens on the incidence of VTE, by comparing 4538 patients with VTE with 5914 controls. Only 3% of patients in the VTE

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Table 2 A randomized trial of rosuvastatin in the prevention of venous thromboembolism—the JUPITER trial; reduction in primary[a] endpoint and venous thromboembolism.

	Rosuvastatin ($n = 8901$)	Placebo ($n = 8901$)	HR (95% CI)	P
Primary endpoint	142 (0.77/100 patients/year)	251 (1.36/100 patients/year)	0.56 [0.46—0.69]	$P < 0.00001$
VTE				
Total VTE	34 (0.18/100 patients/year)	60 (0.32/100 patients/year)	0.57 [0.37—0.86]	$P = 0.007$
Unprovoked VTE	19 (0.10/100 patients/year)	31 (0.17/100 patients/year)	0.61 [0.35—1.09]	$P = 0.09$
Provoked VTE	15 (0.08/100 patients/year)	29 (0.16/100 patients/year)	0.52 [0.28—0.96]	$P = 0.03$
Pulmonary embolism	17 (0.09/100 patients/year)	22 (0.12/100 patients/year)	0.77 [0.41—1.45]	$P = 0.42$
Deep vein thrombosis	17 (0.09/100 patients/year)	38 (0.20/100 patients/year)	0.45 [0.25—0.79]	$P = 0.004$

CI: confidence interval; HR: hazard ratio; VTE: venous thromboembolism.
[a] The primary endpoint was a composite of death, death from cardiovascular causes, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke and arterial revascularization.

group were using a statin, versus 6% in the control group, corresponding to a risk reduction of 45% (OR: 0.55, 95% CI: 0.46—0.67). No risk reduction was seen with use of a non-statin lipid-lowering drug (OR: 0.88, 95% CI: 0.46—1.71). Antiplatelet therapy significantly reduced the risk of VTE by 24% (OR: 0.76, 95% CI: 0.60—0.95), and simultaneous use of aspirin and antiplatelet therapy reduced the risk by 62% (OR: 0.38, 95% CI: 0.25—0.57). The authors also compared the impact of the various statins used on VTE risk. The majority of patients were using simvastatin, atorvastatin or pravastatin, and no difference was found in the risk reduction observed with these three drugs. There were too few rosuvastatin and fluvastatin users to draw any valid conclusions about these statins. The statin doses used were not specified in this study, and it was therefore impossible to determine whether a dose-effect relationship exists. And again, as this was an observational case-control study, the level of evidence it provides is low.

Recently, Ashrani et al. performed a case-control study using the longitudinal population-based resources of the Rochester Epidemiology Project to compare all Olmsted County residents experiencing a first VTE event between 1988 and 2000 with age- and sex-matched controls (one or two controls for each case) [6]. Lipid-lowering therapy was associated with a lower risk of VTE (OR: 0.73, 95% CI: 0.55—0.96; Table 1), and the association was statistically stronger for statins. However, after adjustment for common VTE risk factors, the association remained consistent but not statistically significant (OR: 0.67, 95% CI: 0.43—1.04).

JUPITER was a double-blind randomized placebo-controlled clinical trial in patients with a cholesterol concentration below the accepted threshold for cardiovascular risk (low-density lipoprotein cholesterol < 1.3 g/L) but with high-sensitivity C-reactive protein (hs-CRP) concentrations of 2 mg/L or higher [5]. This patient group was chosen because of the observation that hs-CRP concentration might be a marker for cardiovascular risk. As statins reduce hs-CRP concentrations, the authors postulated that these drugs might reduce the incidence of cardiovascular events in a population whose cardiovascular risk was theoretically low. More than 17,000 patients were randomized to receive either rosuvastatin 20 mg/day or placebo. The primary outcome was the occurrence of a first major cardiovascular event. In JUPITER, rosuvastatin produced a reduction of 44% in the primary endpoint (HR: 0.56, 95% CI: 0.46—0.69; $P < 0.00001$) (Table 2). Analysis of the individual components of the primary endpoint showed a 54% risk reduction for fatal or non-fatal myocardial infarction (HR: 0.46, 95% CI: 0.30—0.70; $P < 0.0002$) and a 48% reduction for fatal or non-fatal stroke (HR: 0.52, 95% CI: 0.34—0.79; $P < 0.002$). Hypothesising that rosuvastatin may also act on venous thrombus formation, the authors prespecified that the frequency of VTE would also be measured in each randomization arm of this trial [12]. A significant result was observed for this endpoint too, with a 43% reduction in VTE events in the rosuvastatin arm (HR: 0.57, 95% CI: 0.37—0.86; $P = 0.007$). The reduction was significant for provoked VTE (HR: 0.52, 95% CI: 0.28—0.96; $P = 0.03$), but non-significant for unprovoked events (HR: 0.61, 95% CI: 0.35—1.09; $P = 0.09$). Rosuvastatin reduced the risk of deep vein thrombosis by 55% (HR: 0.45, 95% CI: 0.25—0.79; $P = 0.004$), but the risk of pulmonary embolism was not significantly reduced (HR: 0.77, 95% CI: 0.41—1.45; $P = 0.42$). Subgroup analysis showed a 50% risk reduction in men (HR: 0.50, 95% CI: 0.30—0.84; $P < 0.05$), but a non-significant reduction in women (HR: 0.74, 95% CI: 0.35—1.56). This difference could be related to the fact that the trial contained more men than women (62% men). A 45% reduction in the risk of VTE was demonstrated in patients aged between 50 and 69 years (HR: 0.55, 95% CI: 0.31—0.96; $P < 0.05$), while the reduction was not significant among participants aged 70—97 years (HR: 0.59, 95% CI: 0.31—1.11). The authors concluded that rosuvastatin reduces the risk of VTE to the same degree as it reduces the incidence of arterial events, and that these two effects are independent. Furthermore, the total number of venous events (94 cases) was similar to the total number of cases of stroke (97 cases) and myocardial infarction (99 cases), showing that, in this population, VTE was as common as these major life-threatening cardiac and vascular events. This study also confirmed that the effect of statins on the incidence of VTE was independent of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride concentrations, a finding consistent with earlier observations that non-statin lipid-lowering agents have no effect on VTE risk. The relatively high dose of rosuvastatin used in this study could argue in favour of a dose-dependent

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Table 3 The main studies that measured the influence of statins on the frequency of recurrence of venous thromboembolism.

Study	Design	HR [95% CI]	Level of evidence[a]
Nguyen et al., 2013 [19]	Population-based cohort; 44,330 patients; 3914 statin users	0.74 [0.68—0.80]	Low
Biere-Rafi et al., 2013 [18]	Population-based cohort; 3093 patients with pulmonary embolism; 737 statin users	0.50 [0.36—0.70]	Low
Schmidt et al., 2012 [20]	Population-based cohort; nested case-control study; 27,862 patients; 3327 statin users	0.72 [0.59—0.88]	Low
EINSTEIN DVT/PE [21]	RCT; post-hoc analysis	0.76 [0.46—1.25]	Low
EINSTEIN extension [21]	RCT; post-hoc analysis	0.81 [0.35—1.86]	Low

CI: confidence interval; DVT: deep vein thrombosis; HR: hazard ratio (representing the risk of venous thromboembolism occurring in statin non-users); PE: pulmonary embolism; RCT: randomized controlled trial.
[a] Levels of evidence are based on the recommendations of the French National Authority for Health (HAS) [33].

effect, consistent with earlier data suggesting a preventive effect for high doses of statins on VTE risk [7]. However, because the effect on VTE is modest, many patients (714 per year) need to be treated in order to prevent one event.

Meta-analyses

The meta-analysis of such disparate studies poses quite a challenge, but several authors have attempted to do so. Agarwal et al. performed a meta-analysis of the observational studies described above, and compared these results with those of the JUPITER trial [13]. The high statistical heterogeneity of these studies reflects their methodological disparity. The authors nonetheless felt able to conclude that the observational studies show that statins reduce the incidence of VTE (−30%), deep vein thrombosis (−40%), and pulmonary embolism (−30%), pointing out that the 43% reduction in the incidence of VTE found in the single randomized trial, JUPITER, had produced similar results. Squizzato et al. conducted a meta-analysis of studies published up to April 2009 that had evaluated the effect of lipid-lowering drugs, including statins and fibrates, on VTE risk [17]. Their analysis included data from a total of 863,805 patients. Statins reduced the risk of VTE by about 20% (OR: 0.8, 95% CI: 0.66—0.99). Again, the statistical heterogeneity among these studies was high. Fibrates were associated with a significant increase in the risk of VTE (OR: 1.58, 95% CI: 1.23—2.02). Pai et al. limited their meta-analysis to four cohort studies and four case-control studies, which supported a reduction in the risk of VTE of about 33% in statin users (OR: 0.67, 95% CI: 0.53—0.84) [15]. The meta-analysis published by Rahimi et al. supports a more modest effect [16]. These authors pooled the results of 22 controlled trials published up to March 2012, including a total of 105,759 participants. It should be borne in mind that VTE was not the primary endpoint of any of these clinical trials and was a secondary endpoint in two trials, including JUPITER. In this meta-analysis, randomization to statin therapy did not significantly reduce the risk of VTE events (OR: 0.89, 95% CI: 0.78—1.01; $P = 0.08$), deep vein thrombosis (OR: 0.85, 95% CI: 0.72—1.01), or pulmonary embolism (OR: 0.92, 95% CI: 0.76—1.12). Exclusion of the results of the JUPITER trial had little impact on the results (OR: 0.93, 95% CI: 0.82—1.07; $P = 0.32$). Finally, there was no evidence that higher-dose statins reduced the risk of VTE events any more than standard doses (198 events [1.0%] versus 202 events [1.0%], OR: 0.98, 95% CI: 0.80—1.20; $P = 0.87$). The results of this meta-analysis do not support the previous observation of a protective effect for statins (or higher-dose statins) against VTE events. However, a more moderate risk reduction of up to about 20% cannot be ruled out. It is clear from these meta-analyses that the difficulty lies in the material available for analysis, due to the heterogeneity of the studies.

In the Cochrane Collaboration analysis of the 36 studies published up to 2013 on the preventive effect of statins against VTE, 35 publications were rejected on the grounds of major methodological limitations (observational studies, post-hoc analyses, case-control studies and cohort studies), with only the JUPITER trial being retained [14]. The main conclusions of this meta-analysis are therefore based on the results of this one trial. The authors point out however that, ideally, further randomized controlled trials would be conducted to confirm the beneficial effect of statins on the incidence of VTE. One obstacle to such a trial is the sheer number of patients that would need to be enrolled. Admittedly, the patients enrolled in JUPITER were considered at low risk, and the incidence of VTE was lower than that observed in an older, less selected population. But even if the frequency of VTE in the placebo group was twice as high, in order to achieve a power greater than 80% and a probability of alpha error of 5%, with follow-up of similar duration to that of JUPITER, it would be necessary to enroll 4900 patients per group to reproduce the effect measured in this trial. This large patient requirement obviously constitutes a major obstacle to the conduct of such a trial.

Statins and secondary prevention of VTE

Given the high frequency of VTE recurrence — up to 10% of patients per year for unprovoked forms — it was logical to evaluate the effect of statins in secondary prevention (Table 3). Three observational studies, based on

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administrative data, have addressed this indication. In a cohort of 44,330 Danish patients diagnosed with VTE, statin use was associated with a significant reduction in the risk of recurrence (adjusted HR: 0.74, 95% CI: 0.68—0.80) [19]. In a population-based registry study conducted in the Netherlands, which linked pharmacy records with hospital discharge reports for patients hospitalized with pulmonary embolism between 1998 and 2008, concomitant use of a statin with anticoagulant therapy was associated with a 50% reduction in the risk of VTE (adjusted HR: 0.50, 95% CI: 0.36—0.70) [18]; this beneficial effect was present both during and after vitamin K antagonist therapy. More recently, Schmidt et al. selected the records of 27,862 patients diagnosed with VTE from a Danish population registry, 3327 of whom were using a statin at the time of diagnosis [20]. Readmission for VTE was 28% less frequent among statin users (adjusted HR: 0.72, 95% CI: 0.59—0.88). The effect was greater among patients receiving statins with high affinity for 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase (rosuvastatin and atorvastatin) than among those using simvastatin or pravastatin.

Using data from patients included in the EINSTEIN deep vein thrombosis/pulmonary embolism (DVT/PE) study, which compared rivaroxaban with the standard curative treatment for VTE, and the EINSTEIN extension study, which compared rivaroxaban with placebo for long-term treatment of VTE, Wells et al. compared the proportion of statin users in each randomization arm [21]. This was a post-hoc analysis, as the original protocol did not set out to address the effect of statins. In EINSTEIN DVT/PE, 1509 patients (18%) were statin users and 6731 (82%) were non-users. The frequency of VTE recurrence during the follow-up period was 2.6% per year ($n = 20$) in the statin group and 3.8% ($n = 146$) per year in non-users. The 24% reduction in the risk was not significant (adjusted HR: 0.76, 95% CI: 0.46—1.25). No difference was found between the patients randomized to receive rivaroxaban or standard treatment. In the EINSTEIN extension study, the absence of events in the ''rivaroxaban with statin'' group precluded comparison with the ''rivaroxaban without statin'' group. Seven events occurred in the ''placebo with statin'' group (12.2% of patients per year), versus 33 in the ''placebo without statin'' group (13.2% of patients per year). The reduction in the risk of VTE was about 20% and not significant (adjusted HR: 0.81, 95% CI: 0.35—1.86). Despite the obvious limitations of their retrospective study, the authors calculated the number of patients that would need to be enrolled in a prospective clinical trial in order to demonstrate a reduction in the incidence of VTE of the same magnitude as in their study (24%), with a follow-up of equivalent duration. A staggering 17,000 patients would be required per group, rendering such a trial unfeasible.

Mechanisms by which statins may prevent VTE

Various hypotheses have been proposed to explain the possible preventive effect of statins against VTE. At the cellular level, statins inhibit isoprenylation of signalling proteins with antithrombotic properties; their effects are characterized by a reduction in both the activity of tissue factor and thrombin generation, attenuation of fibrinogen cleavage, and reduced factor V and factor VIII activity [22,23]. Statins increase the activity of Kruppel-like factor 2 (KLF-2), which promotes the expression of thrombomodulin at the surface of endothelial cells, thereby increasing the activity of the anticoagulant protein C [24].

The involvement of risk factors for atherosclerosis, including dyslipidaemia, in the genesis of venous thrombi is also possible, and would explain in part the putative effect of statins on VTE. Many epidemiological studies have looked for an association between conventional modifiable cardiovascular risk factors (smoking, hypertension, diabetes and dyslipidaemia) and VTE risk [25—28]. These studies showed that the prevalence of atherosclerosis was higher among patients with idiopathic VTE [26]. One meta-analysis showed, for the first time, an association between VTE and each of the risk factors for atherosclerosis [25]. Although the relative risk associated with each risk factor is low, the coexistence of several factors could explain, in part, the causal effect. This interaction between cardiovascular risk factors that participate in the genesis of atheroma and the development of VTE is also illustrated by the results of clinical trials of treatments to prevent cardiovascular disease. In addition to the results of JUPITER discussed above, other studies have shown that administration of low-dose aspirin reduces the recurrence of VTE [29,30]. However, a more recent prospective study in a large cohort of patients has challenged the link between VTE and cardiovascular risk factors [31]. In this study, after 15 years of follow-up, only obesity and smoking were associated with VTE risk. Subclinical markers of atherosclerosis, such as intima-media thickness, have proved equally disappointing [32].

Conclusion

A body of evidence has been acquired that suggests that statins have a preventive effect against VTE. Much of this evidence comes from numerous observational studies, which provide only low-level evidence. A single clinical trial with sufficient power appears to corroborate this preventive effect, but under the specific conditions of this trial (i.e. in a low risk population, where the number needed to treat was very high). Ideally, these results would be confirmed in further trials, in more high-risk patients, if need be. However, these trials would need to include a prohibitively large number of patients. Similar problems apply to secondary prevention, although, in theory, more events would be expected. It is therefore unlikely that any such trials will be conducted in the near future. The proportion of patients taking a statin each day in order to reduce their cardiovascular risk is increasing, and although observational studies will be able to measure indirectly the impact of this practice on VTE, it is unlikely that formal demonstration of the efficacy of statins in this indication will be obtained.

Disclosure of interest

The authors declare that they have no competing interest.

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