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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
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Inhibiteurs de l'hydroxyméthylglutaryl-CoA réductase ;
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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