Statin treatment and the risk of recurrent pulmonary embolism

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This editorial refers to ‘Statin treatment and the risk of recurrent pulmonary embolism’†, by S. Biere-Rafi et al., on page 1800

Statin treatment is well established for the primary and secondary prevention of atherothrombosis in the coronary and cerebral arterial circulation.1 Cholesterol and in particular LDL-cholesterol (LDL-C) is log linearly associated with risk of fatal and non-fatal myocardial infarction; therefore, not unsurprisingly, the benefit of statins on coronary heart disease (CHD) risk appears to be log-linear, with about a one-fifth to one-quarter lowering of CHD risk per 1 mmol/L lowering of LDL-C.1 Whilst the relationship between the effect of cholesterol and LDL-C on incident stroke is less clear, there is clear evidence that statins reduce stroke by about one-fifth, raising the possibility that the clinical benefit may be unrelated to lowering of LDL-C. Statins block hydroxymethylglutaryl (HMG)-CoA reductase, which is a rate-limiting enzyme not only for the production of cholesterol via the squalene pathway but also for the generation of several isoprenoids such as geranyl geranyl pyrophosphate and farnesyl pyrophosphate which prenylate small molecules such as Rho and Ras involved in particular with inflammatory cell signalling, thus leading to activation of various transcription factors.2 These non-LDL-C-dependent but HMG-CoA-related effects have often been referred to as pleiotropic effects and, whilst readily demonstrated in vitro, the clinical relevance of these effects have never been conclusive. Several observational studies and post-hoc data from randomized controlled trials have suggested a range of benefits on cardiovascular disease and the vascular system, from favourable effects on renal function, to favourable effects on heart failure among those with CHD,3 which appear unrelated to effects on LDL-C. It is not surprising, therefore, that interest has focused on venous thrombo-embolic disease.

Biere-Rafi et al. now report on the association between statin exposure and risk of recurrent pulmonary embolism (PE) among individuals with a recent history of PE.4 Using the PHARMO record linkage system in The Netherlands which links community pharmacy records including demographic information with hospital discharge records, the authors were able to create effectively a large cohort study whereby they could study individuals with a prior history of PE and assess the association between exposure to statins and risk of recurrent PE and other cardiovascular outcomes. Among 3093 individuals with a first hospitalization PE between 1998 and 2008, and who received a prescription for a vitamin K antagonist, the adjusted risk of symptomatic recurrent PE was lower by 50% among those taking statins [hazard ratio (HR) 0.50, 95% confidence interval (CI) 0.36–0.70]. Subjects taking statins differed in demographic characteristics and were older, less likely to be male, had a high incidence of cardiovascular disease, were more likely to be diabetic, and were more likely to be taking additional antiplatelet therapy. The unadjusted HR was 0.54, which after full adjustment was minimally attenuated to 0.50, suggesting that the association was not significantly explained by confounding. If exposure to statins was truly protective, one would expect to see greater protection with higher more potent doses. Among individuals exposed to statins which offered a >40% lowering of LDL-C, the adjusted HR was 0.29 (95% CI 0.07–1.16), for those exposed to statins offering a 20–40% lowering, the risk of recurrent PE was 0.44 (95% CI 0.30–0.65), and finally among those receiving statins offering a <20% lowering of LDL-C, the risk was 0.88 (95% CI 0.50–1.54), P for trend <0.001. Taken together with the overall data, this would support a true protective effect. Of interest, the benefit of statin exposure was most marked when vitamin K antagonists were being used, with a HR of 0.22 (95% CI 0.10–0.50), and, although significant, was less marked after discontinuation of vitamin K antagonists (HR 0.69, 95% CI 0.44–0.99), although the authors do not report the interaction P-value. In absolute terms, approximately two-thirds of recurrent PEs occurred after discontinuation of vitamin K antagonists, so while the effect of statin exposure may be attenuated by two-thirds, the higher event rate means that the absolute benefit of statin exposure both during and after vitamin K antagonist therapy is similar and of likely equal clinical importance. These data are consistent with the trial data from the Jupiter trial which showed that rosuvastatin, an agent which reduces LDL-C by

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>50%, resulted in a 43% reduction in first ever venous thromboembolic event. Furthermore, in a meta-analysis of mixed studies, the association between statin exposure and first venous thromboembolic event was lower by about one-fifth.

Finally, if statins indeed exert a true protective effect, what is the major mechanism by which this occurs? Is it related to LDL-C reduction? One way to test this would be to adjust for LDL-C and see if after adjustment the relationship is abolished, or, if enough studies exist, conduct a meta-regression of the difference in LDL-C and benefit across studies. These are both absent, and so we can merely speculate. Unlike arterial atherothrombotic disease, there is little evidence to support a causal association between LDL-C levels and PE or venous thrombo-embolic disease. It is plausible that the non-LDL-C-related effects of statins demonstrated in vitro, ex vivo, or in animal models are indeed clinically relevant. In cell culture, statins increase thrombomodulin (TM) expression on the cell surface, which would result in activation of the protein C pathway, thus counterbalancing the prothrombotic state. Additionally, statins have been shown to reduce tissue factor (TF) expression on endothelial cells via the Rho pathway. Other beneficial effects of statins on coagulation/fibrinolysis include a reduction in circulating levels of von Willebrand factor (vWF), a reduction in plasminogen activator inhibitor (PAI-1), and an increase in tissue plasminogen activator (tPA). Effects on coagulation factors have also been seen, with a reduction in factor VII antigen levels and activity, reduced prothrombin activation, factor Va generation, fibrinogen cleavage, factor XIII activation, and an increased rate of factor Va inactivation. These effects are independent of cholesterol reduction and may serve to reduce clot formation or reduce the stability of fibrin clots. The observation that the protective effect of statins was greatest in relative terms during anticoagulation would support the possibility that the effects of statins on thrombosis may have contributed to clinical benefit.

Other beneficial effects of statins are on nitric oxide (NO) bioavailability. NO not only functions as a vasodilator, but also protects against vascular injury, inflammation, and thrombosis, for instance by inhibiting platelet aggregation. Statins increase NO bioavailability directly via an increase in endothelial nitric oxide synthase (eNOS) and by increasing the stability of eNOS mRNA. Adhesion molecules such as E-selectin and ICAM-1 (intercellular adhesion molecule 1) are expressed on activated endothelial cells, in response to a number of stimuli such as proinflammatory cytokines. Statins reduce the expression of adhesion molecules such as E-selectin and ICAM-1 on the surface of endothelial cells in response to various stimuli. A reduction in adhesion molecule expression results in fewer inflammatory cells binding to an activated endothelium, which in turn reduces local inflammatory cell/platelet aggregates thus reducing the tendency for thrombus formation. In small clinical studies, the use of statins results in a reduction in circulating levels of ICAM-1 and vascular cell adhesion molecule 1 (VCAM-1). Interleukin-1β (IL-1β) and CD40 ligand are inflammatory molecules, which are central to many proinflammatory responses such as adhesion molecule and TF expression in endothelial and inflammatory cells. Both of these cytokines are down-regulated by statin therapy. Treatment with statins results in down-regulation of the inflammatory cytokine IL-1β gene, thus dampening the inflammatory cascade.
clinical findings support earlier cell culture studies which showed that lipophilic statins reduced IL-1β at a transcriptional level in endothelial cells. Taken together, there are multiple biological effects of statins which could plausibly explain a favourable effect on reducing PEs.

In summary, the study by Biere-Rafi et al. adds to the growing weight of evidence that statins have a protective effect on venous thrombo-embolic disease. The effect appears to be large and of clinical relevance, supported by biologically plausible mechanisms and other observational and modest trial data. The current data lend support to the need to conduct a large prospective randomized trial of statins for the secondary prevention of thrombo-embolic disease to establish unequivocally the potential benefits of stains on thrombo-embolic disease.

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**References**


**Corrigendum**


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The name of co-author ‘Manfred Seeberger’ was wrongly displayed as Seeberger Manfred in this manuscript. The authors and publisher apologize for this error.