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Statins and Venous Thromboembolism: The Jury Is Still Out

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Venous thromboembolism (VTE) is a common, potentially fatal, and underestimated condition occurring in 1 per 1000 patients per year worldwide.[1-3] VTE is related either to trauma and immobilization or to increased blood coagulability. Venous thrombosis and VTE are also common after certain types of operations (eg, orthopedic surgery of the lower extremities).[1-3] In many cases, however, VTE is idiopathic.

Several drugs are available for the prevention/treatment of venous thrombosis and VTE, namely unfractionated (UFH) or low-molecular-weight heparin (LMWH), fondaparinux, and oral vitamin K antagonists (ie, warfarin and acenocumarol).[2,3] These anticoagulants are effective, but they require parenteral administration (UFH, LMWH, and fondaparinux) and/or frequent anticoagulant monitoring (eg, for oral vitamin K antagonists). Novel anticoagulants in clinical testing for the prevention of VTE include orally active direct factor II inhibitors (dabigatran etexilate), parenteral direct factor II inhibitors (flovagatran sodium), orally active direct factor X inhibitors (rivaroxaban, apixaban, betrixaban), and ultra-LM WH.[2,3] Dabigatran etexilate and rivaroxaban are already approved for use in atrial fibrillation. In addition, rivaroxaban is approved for VTE prevention following hip and knee replacement surgery.

In the context of statin pleiotropy,[4-8] it has been suggested that these agents may reduce the risk of VTE.[9-15] This effect was reported in a secondary analysis of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), a multicenter double-blind randomized controlled trial (RCT) of rosuvastatin 20 mg/d versus placebo. This trial included 17 802 apparently healthy men (aged $\geq$50 years) and women (aged $\geq$60 years) with low-density lipoprotein (LDL) cholesterol levels <130 mg/dL (<3.4 mmol/L) and high-sensitivity C-reactive protein levels $\geq$2.0 mg/L.[16] Treatment with rosuvastatin was associated with a 43% reduction in the risk of VTE compared to placebo (0.18 vs 0.32 events per 100 person-years of follow-up; hazard ratio [HR] for rosuvastatin = 0.57; 95% confidence interval [CI] = 0.37-0.86; $P = .007$).[16]

A few years ago a systematic review and meta-analysis assessed the effect of statins on the risk of VTE.[17] Overall, 12 studies (n = 850 118 patients) were included: 1 RCT (the secondary analysis of JUPITER),[17] 3 cohort, and 8 case–control studies. Statins decreased the risk of VTE by 19% using the random-effects model analysis (odds ratio [OR] = 0.81; 95% CI = 0.66-0.99).[17] However, there was high heterogeneity among the studies ($I^2 = 88\%$, $P = .04$), which was caused by the case–control and cohort studies. The inclusion of these reports weakened the strength of the meta-analysis. Furthermore, a limitation pointed out by the authors was that the studies included in the meta-analysis "had different inclusion and exclusion criteria, and to combine results across studies may be inappropriate."[17] It follows that the findings of this systematic review should be interpreted with caution.

A recent meta-analysis of 29 RCTs (n = 146 353 participants; 613 800 person-years) failed to support a protective effect of statins (or higher dose statins) on VTE.[18] The primary analyses (restricted to 22 RCTs comparing the effect of statin vs control; 105 759 randomized participants; 422 000 person-years) demonstrated that overall there was no clear evidence that statin therapy reduced the risk of VTE events (465 vs 521, or 0.9% vs 1.0%, for statin users vs controls, respectively; OR = 0.89; 95% CI = 0.78-1.01; $P = .08$). There was no evidence of heterogeneity in the estimated effect size between the trials (heterogeneity $x^2_{21} = 23$; $P = .34$), but a moderate degree of statistical inconsistency between the trials could not be ruled out ($I^2 = 0\%$; 95% CI = 0%-43%).[18]

In the 7 trials that compared a more intensive versus a standard statin regimen (40 594 randomized participants; 191 000 person-years), there was again no evidence that higher statin doses reduced the risk of VTE events compared to standard-dose statin treatment (198 vs 202 or 1.0% vs 1.0%, respectively, OR = 0.98; 95% CI = 0.80-1.20; $P = .87$).

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Furthermore, there was no evidence that the effect varied within these trials (heterogeneity $x^2_6 = 4.5$; $P = .61$). However, a moderate to large degree of statistical inconsistency between the trials could not be ruled out ($I^2 = 0\%$; 95% uncertainty level: 0-61%).[18] Overall, the results from this meta-analysis did not support the suggestion that statins[16] (or higher doses of statins)[12,19] reduce the risk of VTE events substantially, although a more moderate reduction in risk up to about one-fifth could not be excluded.[18]

The more recent meta-analysis had several strengths compared to the previous reports.[18] First, its findings were based on VTE events from several randomized trials (eg.,the Heart Protection Study [HPS],[20] the Stroke Prevention by Aggressive Reduction in Cholesterol Levels [SPARCL] trial,[21] and the Prospective Study of Pravastatin in the Elderly at Risk [PROSPER][22]). Most of these trials had a double-blind design and VTE events had been collected as part of safety and efficacy monitoring. The lack of a substantial reduction of the risk of VTE by statins raised the question whether such an effect may be "too good to be true".[23]

In another recent study, the authors argued that serious methodological weaknesses (eg, selection of controls), as well as different exclusion criteria, limit the establishment of a causal relationship between statin use and risk of VTE.[24] Furthermore, patient adherence to statin treatment should not be underestimated.[25] Approximately, half of the patients receiving statins may discontinue treatment within 6 months.[26] Thus, this study evaluated the association between adherence to statin treatment and VTE prevention in 1 27 822 patients (5 94 190 person-years).[24] The risk of VTE was lower by 19% and 22% in the middle (HR = 0.81; 95% CI = 0.70-0.93; $P = .004$) and highest (HR = 0.78; 95% CI = 0.69-0.89; $P < .001$) compared to the lowest adherence group, respectively.[24]

The side effects associated with statin use (mainly myopathy) may lead to treatment discontinuation.[27-29] The incidence of statin-related myopathy is reported in approximately 10% of the statin-treated patients leading to discontinuation in almost one-third of these patients.[27,28] Statin-related myopathy may be influenced by genetics and tends to be dose dependent.[28] In statin-intolerant patients, potential alternative strategies include switching to a different statin, reducing the frequency of statin administration, substituting statins with other LDL cholesterol-lowering agents (eg, ezetimibe, colesevelam, or nicotinic acid), and combining low-dose statin treatment with other lipid-modifying drugs.[30,31] Another approach is to administer rosuvastatin once or twice weekly.[28] However, whether or not these alternative options have an effect on the risk of VTE remains to be determined.

In conclusion, the conflicting results of the effect of statins on VTE events[12,16,18,19,24] suggest that it may be premature to reach any definite conclusion. The association reported in the recent retrospective cohort study between adherence to statin treatment and the risk of VTE events[21] needs to be considered in the design of RCTs. Statins are a safe treatment option. If VTE is prevented it would add to the benefit of statins and possibly influence the decision making regarding prescribing these drugs.

Declaration of Conflicting Interests

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