



ASH evidence-based guidelines: statins in the prevention of venous thromboembolism

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A 42-year-old woman under your care for the management of obesity calls you because she has a sister who had a pulmonary embolism. The patient recently read that statin medications are associated with a lower risk of venous thromboembolism (VTE) and wonders whether she should take a statin drug to prevent the development of pulmonary emboli.

Hydroxymethylglutaryl-CoA reductase inhibitors, or statins, have been in use for the management of hypercholesterolemia since the late 1980s, when lovastatin became the first such medication approved by the FDA. They inhibit the first enzymatic step in the synthesis of cholesterol by the liver. Additionally, statins have several salutary effects beyond cholesterol lowering, including reduction of inflammation and oxidation,¹ inhibition of platelet aggregation,² and contributing to the balance of procoagulant and fibrinolytic activities.^{2,3} A recent large, randomized, controlled trial showed that rosuvastatin decreased the frequency of symptomatic VTE in patients without coronary disease but with elevated high-sensitivity C-reactive protein.⁴ This confirms reports from two large case-control studies that statins are protective against VTE.^{5,6}

VTE comprises deep-vein thrombosis (DVT) and pulmonary embolism (PE), which have an estimated annual incidence of 121.5 per 100,000 person-years.⁷ Risk factors for VTE may be inherited or acquired; among the former are mutations in the genes for a variety of hemostatic proteins. Acquired risk factors include surgery, immobility, trauma, and hormonal agents such as oral contraceptives and anti-estrogens. Other risk factors for VTE are older age, obesity, hypertension, smoking, and diabetes.

A Medline search was performed combining “venous thromboembolism” (keyword 9397 hits) or “venous thrombosis” (keyword 51,328 hits) and “statins” (keyword 21,823 hits), yielding 60 articles. Fifty-three articles were excluded because they were reviews, editorials, or trials that were not directly relevant; one post-hoc analysis reiterating information from a previous study also was excluded. The remaining papers included one large randomized, con-

trolled trial along with several large case-control and cohort studies. In the randomized controlled trial, 17,802 persons free of known cardiovascular disease (CVD) but with high-sensitivity C-reactive protein (CRP) levels of 2.0 mg/L or more were randomly assigned to rosuvastatin versus placebo, with a prespecified secondary outcome of symptomatic PE or DVT.⁴ Over a median 1.9 years of follow-up, 34 participants in the rosuvastatin arm and 60 in the placebo arm developed VTE, for a hazard ratio of 0.57 (95% confidence interval 0.37-0.86, $P = .007$). Of the total cases of VTE, 47% were provoked.

Table 1 displays the data from this and other published studies. The majority of these reports show that use of statin drugs is associated with a lower frequency of VTE. For example, results of two large case-control studies were published in 2009. In the study by Ramcharan et al of 4538 cases of VTE and 5914 controls, use of any statin was resulted in an odds ratio of 0.55 (95% CI 0.46-0.67),⁵ and in the study by Sorensen et al of 5824 cases of VTE and 58,240 controls, any statin use resulted in an odds ratio of 0.74 (95% CI 0.63-0.85).⁶ Older retrospective cohort studies found similar inverse associations of statin use and VTE, but clearly the study designs are less favorable than a randomized controlled trial or a prospective cohort study, with potential for reporting and measurement bias.

Although there is a growing body of evidence to suggest that statins may be effective in the prevention of VTE, to date there is only one randomized controlled trial, with a select group of subjects that may limit its generalizability to the population at risk for VTE. Clearly, more evidence from randomized controlled trials is needed. With regard to the patient described at the beginning of this review, we would not favor the prescription of a statin at this time,

Table 1. Published studies reporting the frequency of venous thromboembolism (VTE) in statin users and non-users.

Study	Type	No. of participants	Drug	Result
Glynn 2009 ⁴	RCT (secondary outcome)	8901/8901*	Rosuvastatin	HR 0.57 (0.37-0.86) +
Ramcharan 2009 ⁵	Case-control	4538/5914**	Any statin	OR 0.55 (0.46-0.67)
Sorensen 2009 ⁶	Case-control	5824/58240**	Any statin	OR 0.74 (0.63-0.85)
Smeeth 2009 ⁸	Cohort study	129,288/600,241*	Any statin	HR no statin vs. statin 1.18 (1.06-1.31)
Lacut 2004 ⁹	Case-control	377/377**	Any statin	OR 0.42 (0.23-0.76)
Herrington 2002 ¹⁰	Nonrandomized comparison (part of HERS)	1712/1051*	Any statin	HR 0.40 (0.18-0.91)
Yang 2002 ¹¹	Retrospective cohort study	22,993/61,100*	Any statin	IRR current/recent statin use 0.8 (0.3-2.7)
Ray 2001 ¹²	Retrospective cohort study	77,993/47,869*	Any statin	HR 0.78 (0.69-0.87)

Hazard ratios (HR), odds ratios (OR), and incidence rate ratio (IRR) with 95% confidence intervals for comparisons of VTE prevalence in statin users versus non-users*, and statin use or non-use in persons with or without VTE**.

*VTE events/100 person-years.

RCT indicates randomized controlled trial; HERS, Heart and Estrogen/Progestin Replacement Study.

given the lack of high-quality data to support the use of this drug with its appreciable costs, potential side effects, and uncertain benefit (a Grade 2B recommendation based on the ACCP Grading System¹³).

Disclosures

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Off-label drug use: Statins in venous thromboembolism.

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