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INTERPRETING THE JUPITER TRIAL

Statins can prevent VTE, but more study is needed

ABSTRACT

Analysis of a secondary end point of the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) found that a statin reduced the risk of venous thromboembolism (VTE) in apparently healthy people with high levels of C-reactive protein and normal levels of low-density lipoprotein cholesterol (N Engl J Med 2009; 360:1851–1861). Still, pending more study, statins should not be substituted for proven prophylaxis and anticoagulation, especially for patients with recurrent deep venous thrombosis, hospitalized patients, postoperative patients, and other patients prone to VTE.

KEY POINTS

Risk factors for VTE overlap with those for arterial thrombosis, although the data are mixed.

The statin drugs have a number of effects on factors other than lipid levels, notably on markers of inflammation and on clotting factors.

In the JUPITER trial, the incidence of VTE in people taking rosuvastatin (Crestor) 20 mg/day was about half that in people taking placebo. This was a relatively healthy population, and the incidence in both groups was low.

Further study is needed in patients at risk of VTE.

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A major placebo-controlled trial has found that a statin can reduce the risk of venous thromboembolism (VTE).[1]

We do not recommend prescribing this class of drugs for this purpose until much more research has been done, and we certainly do not recommend substituting a statin for anticoagulant therapy in a patient at risk of VTE.

Nevertheless, we are excited by the latest findings, and we find comfort in knowing that if a patient is taking a statin for an approved indication, ie, reducing the risk of cardiovascular disease in a patient with hyperlipidemia or a previous cardiovascular event, the drug will also reduce the risk of VTE.

In the pages that follow, we describe and comment on what is known about the effect of statins on the risk of VTE.

ARTERIAL AND VENOUS THROMBOSIS: HOW ARE THEY LINKED?

The causes of arterial thrombosis may not be entirely distinct from those of deep vein thrombosis and pulmonary embolism, collectively referred to as VTE. Some studies have found that risk factors for arterial thrombosis overlap with those for VTE.[2–4] However, other studies have shown no association between venous and arterial events.[5–10]

Hyperlipidemia, in particular, has been evaluated to see if it is a risk factor for VTE. As with other risk factors for arterial thrombosis, the data have been mixed, with some reports favoring an association with VTE and others not.[4,5,11] Even so, preventive strategies targeting arterial risk factors have shown promise in reducing VTE events.[12]

TABLE 1

Studies of the effect of statins on venous thromboembolism

AUTHORS	STUDY TYPE	STATIN EFFECT
Grady et al[14]	Observational [a]	Hazard ratio 0.5
Ray et al[15]	Observational	Hazard ratio 0.8
Yang et al[20]	Case-control	Relative risk 1.1 (NS) [b]
Doggen et al[16]	Observational	Odds ratio 0.6 (NS)
Lacut et al[17]	Case-control	Odds ratio 0.4
Smeeth et al[21]	Observational	Hazard ratio 1.0
Ramcharan et al[18]	Case-control	Odds ratio 0.5
Sørensen et al[19]	Case-control	Relative risk 0.7

[a] Subgroup analysis of the randomized Heart and Estrogen/Progestin Replacement Study (HERS)
[b] Relative risk 0.8 in a follow-up analysis (NS)
NS = not significant

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Although commonly used to treat hyperlipidemia, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are believed to reduce the incidence of thrombosis by a number of mechanisms[13]:

- Decreasing platelet aggregation
- Inhibiting expression of tissue factor and plasminogen activator inhibitor 1
- Increasing expression of tissue plasminogen activator
- Increasing expression of thrombomodulin, which can activate protein C and prevent thrombin-induced platelet and factor V activation and fibrinogen clotting.

STATINS AND VTE IN OBSERVATIONAL AND CASE-CONTROL STUDIES

In view of the multiple effects of statins, several studies have looked at whether these drugs reduce the occurrence of both arterial thrombosis and VTE.[14–19]

Two prospective observational studies and four case-control studies found that statins reduced the risk of VTE by 20% to 60%.[14–19] Interestingly, two of the case-control studies found that antiplatelet therapy did not reduce the risk of VTE.[18,19]

However, retrospective studies published in 2002[20] and 2009[21] found no statistically significant reduction in the incidence of VTE in statin users vs nonusers (TABLE 1). Observational and case-control studies, though, can have biases and confounders that may go unrecognized without rigorous prospective investigation.

THE JUPITER STUDY

The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study primarily sought to determine if rosuvastatin (Crestor) 20 mg/day, compared with placebo, would reduce the rate of first major cardiovascular events.[22] A prespecified secondary end point of the trial was VTE, making JUPITER the first randomized, placebo-controlled trial to specifically test whether statins prevent VTE.[1]

Inclusion criteria: Normal LDL, high CRP

The study included men age 50 and older and women age 60 and older with no history of cardiovascular disease. In addition, their low-density lipoprotein (LDL) cholesterol levels had to be lower than 130 mg/dL (3.4 mmol/L), their triglyceride levels had to be lower than 500 mg/dL (5.6 mmol/L), and their high-sensitivity C-reactive protein (hs-CRP) levels had to be 2.0 mg/L or higher.

Since high levels of hs-CRP, a marker of inflammation, predict cardiovascular events and since statins lower hs-CRP levels, the investigators hypothesized that people with elevated hs-CRP but without hyperlipidemia might benefit from statin treatment.[21]

Patients were excluded if they had received lipid-lowering therapy within 6 weeks of the trial screening, had diabetes mellitus or uncontrolled hypertension, were currently using postmenopausal hormone-replacement therapy, or had had cancer within the previous 5 years, except for certain skin cancers.

Candidates who complied well during a 4-week placebo run-in phase were randomly assigned to receive either rosuvastatin 20 mg

daily (an intermediate dose) or a matching placebo. In all, 17,802 people were randomized. The two assigned groups appeared to be well matched.

Patients were to come in for visits twice a year for 60 months after randomization to be assessed for symptomatic deep venous thrombosis and pulmonary embolism. New cases of VTE were confirmed by imaging studies, by the initiation of anticoagulation therapy, or by death ascribed to pulmonary embolism.

Idiopathic VTE was classified as *unprovoked* if it occurred in the absence of trauma, hospitalization, or surgery within 3 months before the event, and in the absence of any diagnosed cancer within 3 months before and after the event. *Provoked* VTE events were those that occurred in a participant with cancer or when a precipitating event was associated with trauma, hospitalization, or surgery.

Rosuvastatin prevents heart attack, stroke

On the recommendation of the trial's independent data and safety monitoring board, JUPITER was stopped early because the trial drug showed evidence of efficacy in preventing the combined primary end point of a first major cardiovascular event—ie, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from a cardiovascular cause.[22] (The cardiovascular outcomes of the JUPITER study were reviewed by Shishehbor and Hazen[23] in the January 2009 issue of the *Cleveland Clinic Journal of Medicine*; see doi:10.3949/ccjm.75a.08105).

Formal follow-up for the trial's primary and secondary efficacy end points ended then, but data on VTE continued to be collected until each patient's closeout visit as part of a safety monitoring protocol. The last closeout visit occurred on August 20, 2008. The primary analysis focused on events occurring up to March 30, 2008, the date the study was stopped.

Secondary end point results: Rosuvastatin prevents VTE

At a median follow-up of 1.9 years, an episode of VTE had occurred in 94 (0.53%) of the 17,802 patients—34 in the rosuvastatin group and 60 in the placebo group.[1] This translates to 0.18 and 0.32 events per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for the rosuvastatin group 0.57, 95% confidence interval [CI] 0.37–0.86, $P = .007$).

Forty-four cases of VTE were classified as provoked and 50 cases were categorized as unprovoked. The risk reduction was statistically significant for provoked cases (hazard ratio 0.52, 95% CI 0.28–0.96, $P = .03$), but not for unprovoked events (hazard ratio 0.61, 95% CI 0.35–1.09, $P = .09$).

Subgroup analysis revealed no significant association between patient characteristics and the impact of rosuvastatin on the risk of a VTE event, but, as expected, more benefit was associated with higher baseline lipid levels.

STILL TOO SOON TO ADVISE ROUTINE STATIN USE TO PREVENT VTE

While the JUPITER trial data show an apparent benefit of statin use on the rate of VTE events, advising routine use of statins to prevent VTE is premature, for three main reasons.

Many must be treated to prevent one case of VTE. The number needed to treat (NNT) with rosuvastatin for 5 years to prevent either a case of VTE or a cardiovascular event was 21, and the NNT to prevent one cardiovascular event was 25. In a review of the two most recent case-control studies investigating the effects of statins on VTE,[18,19] Cushman[24] calculated that the NNT to prevent one VTE event each year was 333 for those age 75 and older. Though the JUPITER data did not provide the specific incidence of VTE at 1 year, except graphically, we can estimate that the NNT to prevent one VTE event at 1 year in the study is also very high.

Statins should not be substituted for proven prophylaxis and anticoagulation, pending further investigation

Practically speaking, the perceived benefits of VTE prevention require large numbers to be treated, and the net clinical gain is still largely in preventing arterial events such as heart attack and stroke rather than VTE.

Statins, though safe, can still have adverse effects. The JUPITER study found a trend (albeit nonsignificant) toward more muscle complaints and elevations on liver function testing in apparently healthy persons taking a statin.[22] Although severe complications of statin therapy such as rhabdomyolysis

and elevations of creatine phosphokinase are rare, patients taking a statin have a 39% higher risk of an adverse event, most commonly myalgias or abnormalities on liver function testing.[25] Were statins to be given routinely to even more people than they are now, more adverse outcomes would be likely.

More study is needed. The JUPITER study did not address a high risk of VTE. In fact, the investigators provided no information as to the VTE history of those enrolled.

Clearly, statins should not be substituted for proven prophylaxis and anticoagulation without further investigation, especially for patients with recurrent deep venous thrombosis, hospitalized patients, postoperative patients, and other patients prone to VTE.

OUR VIEW

The JUPITER study is an important leap forward in adding to our knowledge of how to prevent VTE. For people with another indication for taking a statin (eg, a previous cardiovascular event, hyperlipidemia), it is helpful to know that their risk of VTE may be reduced without exposure to the risks of other kinds of conventional thromboprophylaxis.

We look forward to additional studies to elaborate on the benefits of statins in both the prevention and treatment of VTE for average-risk and VTE-prone populations.

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