HMG CoA reductase inhibitors and the risk of venous thrombosis among postmenopausal women

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See also Ray JG. Do we care if statins prevent venous thromboembolism? This issue, pp. 695–6.

In addition to lowering blood lipid levels, statins (HMG CoA reductase inhibitors) inhibit platelet aggregation and maintain a favorable balance between prothrombotic and fibrinolytic mechanisms [1]. Perhaps these effects may account for the association of statins with a reduced risk of venous thrombosis [2,3]. Because different statins have different properties [4], the possibility that the risk of venous thrombosis varied by specific statin was also investigated.

A population-based case-control study was conducted at Group Health Cooperative (GHC), a large health maintenance organization in western Washington state, USA. Cases were all postmenopausal women aged 30–89 years who had a first venous thrombosis between January 1, 1995 and December 31, 2000. This particular case-control study is one of several on-going case-control studies that share a single control group, which presents a stratified random sample of postmenopausal female Group Health members. For historical and sample-size reasons, the controls were frequency matched on age, calendar year of identification, and treated hypertension status to distributions of myocardial infarction cases [5]. The index date for cases was the date of their first venous thrombosis, while for controls it was a random date during the calendar year in which they were selected to participate. We used GHC computerized pharmacy records to ascertain current use of lipid lowering medications at the index date, and categorized women into non-users of lipid lowering medications; statin users; and users of other lipid lowering medications, including bile-acid sequestrants, fibrates and niacins. Current use was defined as the receipt of at least one lipid lowering prescription prior to the index date with enough medications to last until the index date, assuming 80% compliance. Duration of use was calculated as the number of days that each prescription would last assuming 80% compliance and by summing this for each prescription since starting date. Simvastatin and pravastatin were used by 97.8% of the current statin users. Three women who used other statins (lovastatin or atorvastatin) and 17 women with chronic liver disease were excluded from the analysis. Women prescribed less than 40 mg of simvastatin were defined as low-dose users, and women prescribed 40 mg or more were defined as high-dose users.

Included in this study were 465 postmenopausal women with a first venous thrombosis and 1962 controls. Venous thrombosis was objectively verified with a venogram, Doppler or Duplex study, a pulmonary angiography, lung scan with a high probability, or a computer tomography scan in 93% of all cases. Of the remaining 32 women, 13 died before any diagnostic test or treatment could be started and 19 women were treated with coumadin or had a vena cava filter after the diagnosis of venous thrombosis was clinically made. Deep vein thrombosis (DVT) in the leg occurred in 348 cases, a pulmonary embolism (PE) in 42, and 75 cases were diagnosed with both DVT and PE.

At the index date, 4.5% of cases and 5.6% of controls were current users of statins. The median duration of statin use among cases was 435 (range 13–1751) days as compared to 354 (range 4–2505) days among control subjects. Among current users, 76.2% of cases and 85.5% of controls used simvastatin. Current statin users appeared to have a slightly lower risk of venous thrombosis than non-users after adjustment for the matching factors (OR 0.84; 95% CI 0.51–1.37) (Table 1).

Adjustment for current estrogen use did not alter any of the odds ratios, in contrast to adjustment for vascular disease which decreased the risk. Further adjustment for weight and height or diabetes did not substantially effect the odds ratios. The reduced risk of venous thrombosis seemed to be confined to women using simvastatin as opposed to pravastatin and was found among both low-dose and high-dose users of simvastatin. Because of time trends in use direct comparison
between individual statin medications may not be reliable, but the comparison suggested a decreased risk of venous thrombosis for simvastatin compared to pravastatin users (OR adjusted matched factors 0.14; 95% CI 0.02–0.88).

The study results suggest that statins may reduce the risk of venous thrombosis, as has been found before [2,3]. However, there seems to be heterogeneity between the individual statin medications, and in this study only simvastatin was associated with a decreased risk. Several mechanisms, other than chance, may explain this potential heterogeneity. First, in vitro, the lipophilic simvastatin suppresses tissue factor activity and antigen and tissue factor expression in macrophages, an effect not found with the hydrophilic pravastatin [6]. As tissue factor initiates blood coagulation, it may act as a risk factor for venous thrombosis. Secondly, simvastatin treatment impairs activation of prothrombin, factor (F) V and FXIII, and enhances FVa inactivation by activated protein C [7], which may lead to a reduced risk of venous thrombosis. To our knowledge, the effect of pravastatin on these factors has not been reported. Finally, the disparate findings for individual statin medications may be due to differences in metabolism [4]. One limitation of this study is the low power. While there are several plausible biologic explanations for the differences in venous thrombosis risk found between individual statins, these suggestive findings need to be replicated in other populations.

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