Statins, platelets, and the elderly

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As a class of drugs, statins have gained renown for their ability to effectively reduce cardiovascular events in both patients with heart diseases (secondary prevention) and in those who, while not with manifest heart disease (primary prevention), are at increased risk based on a variety of risk factors including hypertension, diabetes, and age.

Statins are reversible in inhibitors of the enzyme HMG-CoA reductase, the enzyme which converts HMG-CoA to mevalonate. This is an early rate-limiting step in the biosynthesis of cholesterol by the liver. Inhibition of HMG-CoA reductase by statins decreases intracellular cholesterol biosynthesis, which leads to upregulation of the low-density lipoproteins(LDL) receptors on the cell surface, and subsequently an increased uptake of LDL remnants from the systemic circulation. By this mechanism, statins lower serum LDL and raise HDL. The predominant benefits of statins on CHD risk reduction is due to their effects on LDL-C, but the effects that statins have on triglycerides and high-density lipoproteins (HDL) may also contribute to the risk reduction.

It has become clear, however, that the benefits of statins extend beyond simply effects of LDL lowering and HDL rising. Clinical outcomes trials including the PROVE-IT trial and MIRACL show clinical event reduction well before what would be expected based on effects of lipid modification on atherogenesis. These trials and many others have contributed to the greatly expanding data confirming the pleiotropic effects of statins. In addition to their effects on lipids, statins act to inhibit the proliferation, migration and signaling of vascular smooth muscle cells, affect endothelial function, inflammation, coagulation and plaque vulnerability.

An interesting area of research and the topic of the paper appearing in this issue of the Journal of Geriatric Cardiology are the effects that statins exert on platelet function. It is well known that hypercholesterolemia is associated with platelet dysfunction. Platelet activity is enhanced and may be a factor critical to the pathogenesis of atherosclerotic plaque formation. Activated platelets tend to aggregate and are formed close to atherosclerotic plaques as demonstrated in patients who died from myocardial infarction.

High levels of LDL interact with platelets to initiate atherosclerotic plaque formation in many ways. First, LDL increases platelet sensitivity to several naturally occurring agonists by the binding of apoB-100, the main lipoprotein in the LDL particle, to a receptor on the platelet membrane. Additionally oxidized LDL leads to the formation of lysophosphatidic acid which generates platelet activating particles. Finally, the transfer of lipids to the platelet membrane increases platelet sensitivity.

Statins exert their effects on platelets by, firstly, lowering LDL and with it reducing the effects discussed above including the hypercholesterolemia mediated platelet dysfunction. Puccetti et al showed that simvastatin treatment significantly reduced platelet P-selectin expression and platelet aggregation after six weeks of treatment. Hwang et al reported short term use of atorvastatin in hypercholesterolemic patients resulted in significant suppression of CD40-CD40L interaction and P-selectin expression.

In their paper in the current issue, Chen et al evaluate the effects of platelet activation in elderly Chinese patients with hypercholesterolemia. Fifty otherwise healthy older patients with hypercholesterolemia (LDL-C 140 mg/dl) received 4 weeks of simvastatin 20mg/day (n=50; average age 65 years) or in those with “normal” cholesterol (n=50; LDL-C 97 mg/dl; average age 65 years) received nothing. Serum lipids, CD63 and CD41a levels as well as other laboratory values were obtained at the start in all subjects and at the end of the four weeks in the treatment group. Subjects were excluded if they had coronary artery disease or cerebrovascular disease or if taking any medications (especially aspirin) that were felt to affect lipid and platelet activity. Not surprisingly, simvastatin 20 mg resulted in an average 30% reduction in serum LDL in the treatment group. There was significant decrease in platelet activity in the treatment group from baseline as measured by CD63 and CD41a activity via fluorescent-signed monoclonal antibodies and using flow cytometry. Interestingly, CD41a activity in the treatment group remained higher than the control.
group despite similar LDL-C levels after treatment. What this suggests is unclear. It may indicate additional lipid lowering may be needed to achieve further platelet inhibition in this at risk group. It would have been instructive to have seen additional subjects treated with either higher doses of simvastatin or perhaps a dose titration with repeat measurements, in order to evaluate for a dose effect of statins on platelet activity. Moreover, repeat measurements of lipids and platelet activity in the control group, to attempt to control effects of diet and other factors influencing subjects enrolled in a study, would have been helpful. Still, there does seem to be a change in these markers of platelet activity.

The effects of statins on markers of platelet activity have been seen previously. Huhle et al 4 investigated the effects of lipid-lowering therapy on the activity of platelets as measured ex vivo by the surface activation markers CD62 (PADGEM, P-selectin, GMP 140) and CD63 (GP53) in a double-blind, randomized, placebo-controlled study. In addition to reducing serum LDL-C concentration by 30% (P<0.01) and total cholesterol by 25% (P<0.01), fluvastatin (40 mg/day) significantly decreased platelet membrane activation markers by 22% and 13% (P<0.05), respectively.

Nomura et al 7 investigated the effects of losartan and simvastatin on circulating levels of platelet activation markers, microparticles, soluble selectins, and soluble cell adhesion molecules in hypertensive and hypercholesterolemic patients with or without Type 2 diabetes. In 25 normotensive healthy controls and 41 hypertensive patients, the angiotensin receptor blocker losartan was administered for 24 weeks and, in the subgroup that also had hypercholesterolemia, simvastatin was administered for the same 24 weeks. This combination resulted in significantly decreased levels of CD62p, CD63, PAC-1, PDMP, EDMP, sE-selectin and sVCAM-1, especially in those patients with Type 2 diabetes. Additionally, the CD63 and PDMP levels were positively correlated with the LDL level before and after treatment in both patients with and without diabetes.

Lastly, the importance of aggressive management in the elderly should be emphasized. The elderly are at particularly high risk for the development of cardiovascular disease and with it there is a dramatic increase in the rates of arterial and venous thrombotic events. Aging is associated with changes in platelet function. Platelets from elderly patients may be less susceptible to inhibition by prostacyclin (PGI2). Von Willebrand factor (vWF) enhances platelet interactions with the damaged endothelium or subendothelium, and vWF levels increase with age. There is an age-related alteration in platelet transmembrane signaling and second messenger accumulation as well. Activated platelets accelerate thrombin generation by providing a major site for thrombus formation. Classically underrepresented from clinical studies and under treated in clinical practice, there are abundant data to support the role of statins in the elderly. A retrospective analysis 3 of Ontario, Canada residents aged 65 years and older found a lower rate of deep venous thrombosis in those receiving statins. Most recently, the PROSPER 10 trial evaluated effects of pravastatin in an elderly population (age 70-82 years) with a history of, or risk factors for, vascular disease. After a follow-up averaging 3.2 years, there was a significant reduction in the primary endpoint of composite coronary death, non-fatal myocardial infarction. It is certainly possible that the benefit seen in these older patients may, in part, be attributed to the effects on platelet function. The study by Chen et al offers a possible explanation as to this mechanism.

References