Editorial

Statin therapy: new therapy for cardiac microvascular dysfunction

Robert S. Rosenson*

Preventive Cardiology Center, Division of Cardiology, Departments of Medicine and Preventive Medicine, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

Received 12 August 2003; accepted 21 August 2003

See doi:10.1016/S1095-668X(03)00478-0, for the article to which this editorial refers

Cardiac syndrome-X is a clinical entity characterized by angina-like chest discomfort that is often prolonged in duration, normal coronary arteries as assessed by arteriography, non-inducible coronary vasospasm with ergonovine provocation and ST segment depression on treadmill exercise testing. The pathogenesis of cardiac syndrome-X has been ascribed to myocardial ischaemia that may be caused by microvascular dysfunction and increased sensitivity to intracardiac pain. Support for impaired myocardial perfusion in the aetiology of chest pain was provided in a case-control study of 20 patients with established syndrome-X and 10 matched controls that underwent cardiac magnetic resonance imaging at rest and after adenosine infusion.1 In syndrome-X patients, adenosine infusion reduced the subendocardial to subepicardial myocardial perfusion index and provoked chest pain in 19 of 20 patients.

The mechanisms that may contribute to microvascular dysfunction in syndrome-X include endothelial dysfunction, and abnormal vasoconstrictive responses of the microvasculature to nitric oxide and endothelin. Several lines of evidence support impaired nitric oxide production or endothelial release by coronary vessels of syndrome-X patients. Intracoronary infusions of acetylcholine induce a diminished vasodilator response in syndrome-X patients compared to controls or may induce myocardial ischemia in the absence of vasospasm in epicardial coronary arteries. The acetylcholine-induced ischemia may result from a vasoconstrictor effect of acetylcholine on vascular smooth muscle cells. In contrast, intracoronary infusions of L-arginine, the precursor of nitric oxide, enhance coronary vasodilation in response to acetylcholine. Further, levels of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide, are increased in syndrome-X patients.²

Therapeutic approaches for patients with syndrome-X include short-term symptom relief with sublingual nitrates, and potentially longer-term use of beta adrenergic blockers or calcium channel antagonists. Beta blockers and calcium antagonists have been shown to reduce the frequency and lessen the severity of chest pain and improve exercise tolerance. Estrogen-replacement therapy has been shown to reduce the frequency of anginal episodes in postmenopausal women presumably by improving endothelium-dependent coronary vasodilation. In this issue of the Journal, Kayikcioglu and colleagues present the results of a clinical trial in syndrome-X patients that investigated whether statin therapy changed endothelial function as measured by flow-mediated dilatation of the brachial artery, and exercise-induced ischemia.³ Forty patients with well-characterized features of syndrome-X were randomly assigned to pravastatin (40 mg daily) or placebo for 3 months. The study patients included predominantly middle-aged women with LDL cholesterol levels <4.2 mmol/l and fasting triglycerides <2.3 mmol/l. It is important to consider that these patients would not be considered for cholesterol lowering therapy according to expert guidelines for cholesterol management. After 3 months, pravastatin-treated patients had a modest 16% lowering of LDL cholesterol (3.1±0.65 mmol/l to 2.6±0.47 mmol/l). There were no significant changes in other plasma lipids. Statin therapy resulted in significant improvements in flow-mediated vasodilatation, exercise duration and time to 1 mm ST segment depression. Ischemic episodes were completely resolved in 26% of statin-treated patients. Total exercise duration correlated with the reduction in LDL cholesterol (r=0.65). Unfortunately, there was no measurement of myocardial ischaemia such as by cardiac magnetic resonance imaging. Other biochemical parameters that improved with pravastatin therapy include fibrinogen and high-sensitivity CRP.

Statin therapy has shown consistent benefits in reducing ischaemic cardiac events in patients with...
angiographically documented coronary stenoses and recurrent ischaemic events in patients with established coronary heart disease. In coronary artery disease patients, statins restore maladaptive remodelling of atherosclerotic coronary vessels, reduce the propensity of unstable plaques to fissure or rupture, improve myocardial perfusion in ischaemic zones and reduce the frequency and severity of ST-segment depression as assessed by ambulatory electrocardiography monitoring.

In this study of syndrome-X patients, statin therapy improved endothelial function and reduced or eliminated cardiac ischaemic episodes in patients with no angiographic evidence of coronary atherosclerosis as determined by the absence of luminal irregularities. Of course, it is well established that intravascular ultrasonography may detect atherosclerosis in the absence of a luminal stenosis, and the absence of this data is one limitation of the current study. Nevertheless, these provocative findings have relevance not only for the long-term management of syndrome-X patients, but as therapy for microvascular disease in general.

Are the findings that statin therapy ameliorates microvascular dysfunction consistent with experimental and clinical studies with this cardioprotective class of lipid-lowering agents? Statins afford vascular protection predominantly through lipoprotein-mediated changes and to a lesser extent non-lipoprotein-mediated processes. The effects of statins on endothelial-dependent vasomotion and blood rheology will be discussed in relation to microvascular disease.

Endothelium-dependent vasodilatation in human coronary arteries correlates with the susceptibility of LDL to oxidation. There are many factors that influence the susceptibility of LDL to oxidation including the size and composition of LDL and the susceptibility to oxidative modification. Oxidative stress inactivates nitric oxide and decrease the expression of endothelial nitric oxide synthase (eNOS) by reducing the stability of eNOS mRNA. Oxidized LDL has also been shown to down-regulate eNOS in human coronary artery endothelial cells through an effect associated with up-regulation of the lectin oxidized LDL (LOX-1) receptor. Various enzymes identified in atherosclerotic lesions have been implicated in the oxidation of LDL in the sub endothelial space. These enzymes include nicotinamide adenine dinucleotide (NADPH) oxidase, 12/15 lipoxigenase, and NO synthase among others. Statins reduce levels of superoxide radicals, an effect that is only partially explained by a reduction in LDL cholesterol. Statins downregulate the expression of LOX-1 and attenuate the effect of oxidized LDL on nuclear factor-kappa B. In addition, statins reduce the cholesterol content and increase lipoprotein fluidity that may reduce the susceptibility of lipids to oxidation. The activity of the HDL-associated antioxidant paraoxonase is increased during statin therapy in familial hypercholesterolemic patients. Statins have also been shown to attenuate angiotensin II induced free radical generation by vascular smooth muscle cells through inhibition of NADPH oxidase subunits p22phox and nox1.

Several cholesterol-independent effects of statins involve inhibition of Rho/Rho kinase. An essential step in the activation of Rho is the posttranslational attachment of geranylgeraniol. Statins inhibit the formation of isoprenoid products of the cholesterol biosynthetic pathway such as geranylgeraniol. Rho-kinase mediated pathways have a central role in endothelial dysfunction and vascular smooth muscle cell hypercontraction. The expression and activity of eNOS is inhibited by Rho/Rho-kinase and this inhibition is blocked by statins. Intracoronary infusion of an inhibitor of Rho-kinase to microvascular angina patients reduced anginal episodes, ST-segment depression and lactate production during infusions of acetycholine. It is possible that statins reduce vascular smooth muscle cell vasospasm through inhibited formation of isoprenoid intermediates in the cholesterol biosynthetic pathway.

Vasoactive substances such as endothelin (ET)-1, thromboxane A2 and angiotensin II contribute to the exaggerated vasoconstriction of atherosclerotic human vessels. ET-1 produced by endothelial cells and inflammatory cells binds to receptors on vascular smooth muscle cells to mediate vasoconstriction. Oxidized LDL increases the expression and release of ET-1. Statins have been shown to reduce pre-pro-ET-1 mRNA expression in vascular endothelial cells by inhibiting Rho geranylgeranylation, and reduce fibroblast growth factor induced expression of endothelin receptors in rat aortic smooth muscle cells. In addition, statins inhibit angiotensin II mediated generation of reactive oxygen species by polymorphonuclear cells and aortic smooth muscle cells.

Blood viscosity has its greatest impact on reducing blood flow in small calibre vessels. Lowering concentrations of plasma lipoproteins and fibrinogen will reduce blood viscosity that may improve blood flow particularly in the microvasculature. Although the modest reductions in plasma lipids with pravastatin would not be expected to reduce blood viscosity, but the 17% lowering of plasma fibrinogen may have a clinically significant effect on microcirculatory flow.

In summary, statins improve endothelial function and alleviate myocardial ischaemia in cardiac syndrome-X patients. The modest reductions in LDL cholesterol reported in this study suggest that cholesterol-independent effects of statins may be important in yielding clinical benefits in the treatment of microvascular disorders. Thus, statin therapy should be considered a useful adjunct in the treatment of cardiac syndrome-X.

References