Cardiovascular Benefit of Cholesterol-Lowering Therapy
Does Improved Endothelial Vasodilator Function Matter?

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Lipid-lowering therapy with HMG-CoA reductase inhibitors (statins) has been shown in large clinical trials to reduce cardiovascular morbidity and mortality in otherwise healthy hypercholesterolemic subjects and in patients with coronary artery disease. The magnitude of risk reduction is greatest in individuals with the highest pretreatment cholesterol levels, although those with mild elevation in LDL cholesterol may also benefit from statin therapy. Because angiographic trials with lipid-lowering therapy have shown little reduction in atherosclerotic plaque size, alternate mechanisms of therapeutic benefit to the arterial wall have been proposed, the most testable of which is improvement in endothelial vasodilator function.

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Endothelial Vasodilator Function Testing, Myocardial Ischemia, and Cardiovascular Risk

The endothelium maintains a nonthrombogenic surface for blood flow, prevents platelet and leukocyte adhesion to the vessel surface, modulates cellular composition of the arterial wall, and promotes dilator tone of arteries and veins, homeostatic properties regulated in part by the local synthesis of nitric oxide. Several groups have shown that endothelial release of nitric oxide is reduced or absent in patients with atherosclerosis, as well as in patients with risk factors for atherosclerosis, including hypercholesterolemia. Thus, acetylcholine, the agonist used in Furchgott and Zawadzki’s experiments that showed release of relaxant factor from the endothelium, commonly constricts coronary arteries of patients with atherosclerosis at doses that dilate arteries of patients whose coronary angiograms appear normal, especially if they are free of risk factors for atherosclerosis. Consistent with the notion that an important mechanism of cardiovascular risk reduction with statin therapy is improvement in nitric oxide–regulated endothelial function, several groups have shown that statin therapy reduces the constrictor effect of acetylcholine on coronary arteries of patients with atherosclerosis and hypercholesterolemia. Increased nitric oxide bioactivity would be expected to restore arterial homeostasis, including arterial dilator responsiveness, which, in turn, might reduce stress-induced ischemia. Thus, improved endothelium-dependent dilator responsiveness after statin therapy, demonstrated by provocative testing and clinically manifest as reduced ischemia during stress, has been viewed widely as a useful mechanistic surrogate for reduced cardiovascular risk by that therapy.

However, in this issue of Circulation, investigators of the Coronary Artery Reactivity After Treatment with Simvastatin (CARATS) study found no benefit of simvastatin 40 mg/d for 6 months to coronary artery epicardial or microvascular endothelial vasodilator function in 34 analyzable patients with mild to moderate coronary artery disease randomly assigned to this therapy, compared with 26 analyzable patients randomized to placebo in a double-blind clinical trial. Participants were mildly hypercholesterolemic (average LDL cholesterol 130 mg/dL) and had not been on cholesterol-lowering therapy for at least 6 weeks before study. Simvastatin at this dosage reduced LDL cholesterol levels by an average of 40% from pretreatment baseline values. Coronary endothelial function was assessed by epicardial diameter and blood flow responses to acetylcholine and to substance P (which, unlike acetylcholine, has no constrictor effect on smooth muscle). Measurements made after 6 months of assigned therapy were compared with respective pretreatment baseline values. In both simvastatin- and placebo-treated groups, there was no difference in the changes in acetylcholine-induced constriction or in substance P–induced dilation of epicardial arteries from baseline values, and similar increases in coronary blood flow were measured in response to these agonists.

Several considerations might be important in accounting for this negative study. First, the average baseline LDL cholesterol was lower in these patients than in participants in previous studies that showed improvement in coronary endothelial vasodilator function with statin therapy. Thus, further reduction in LDL cholesterol with drug therapy may not benefit endothelium that is possibly only mildly dysfunctional. However, CARATS patients had epicardial constriction responses to acetylcholine and limited coronary flow responses to acetylcholine and to substance P, similar to responses described in other studies and consistent with endothelial dysfunction at baseline. Furthermore, cholesterol reduction with statin therapy in patients with similar cholesterol levels to those of CARATS patients reduced risk of fatal coronary events or nonfatal myocardial infarction in the Cholesterol And Recurrent Events (CARE) trial and reduced ischemic events compared with coronary angioplasty.
improved endothelial vasodilator function and vice versa. However, effects of estrogen on exercise-induced ischemia in women with coronary artery disease in randomized, double-blind, placebo-controlled trials have been conflicting.\(^{14,15}\) Furthermore, the Heart Estrogen/progestin Replacement Study (HERS) determined no reduction in cardiovascular events (nonfatal myocardial infarction or cardiovascular death) in postmenopausal women with coronary artery disease and raised concern about an early increase in nonfatal myocardial infarction or cardiovascular death in women treated with hormone therapy relative to placebo-treated women.\(^{16}\) Thus, in women with coronary artery disease, estrogen has inconsistent effects on inducible ischemia and may have biological effects independent of endothelial vasodilator function (eg, coagulation activation, inflammation) that may increase the risk of coronary thrombosis.

**Vitamin E Therapy**

Vitamin E (\(\alpha\)-tocopherol) has been shown to improve endothelial dilator responsiveness in humans, presumably by reducing vascular oxidant stress and increasing nitric oxide bioactivity. Despite enthusiasm for vitamin E therapy based on reduction in nonfatal myocardial infarctions (but not cardiovascular mortality) in the Cambridge Heart Antioxidant Study (CHAOS),\(^{17}\) other clinical trials, including the GISSI-Prevenzione\(^{18}\) and the Heart Outcomes Prevention Evaluation (HOPE) trials,\(^{19}\) reported no reduction in cardiovascular events in patients with established coronary artery disease or at high risk for coronary artery disease compared with placebo treatment.

**L-Arginine Therapy**

L-Arginine, the substrate for nitric oxide synthase, has been shown in several studies to improve endothelial vasodilator function when administered into systemic or coronary arteries of patients with coronary artery disease or hypercholesterolemia. However, acute administration of L-arginine did not improve exercise duration or ST-segment depression in patients with coronary artery disease, despite improvement in endothelium-dependent vasodilation in response to acetyl-
choline. Whether chronic L-arginine therapy reduces risk of cardiovascular events remains to be determined.

Thus, these 4 therapies, all of which improved endothelium-dependent vasodilation in humans (including patients with coronary artery disease) do not consistently reduce myocardial ischemia and/or cardiovascular risk. Accordingly, improvement in endothelial function as currently determined by dilator responses to infused agonists or to shear stress may have limitations as a surrogate for determination of potential vasculoprotective effects of a therapy. Furthermore, coronary artery endothelial testing carries risk of injury, even in experienced hands, as evidenced in a CARATS study participant.

With regard to statin therapy, other biological effects may be of greater importance than coronary endothelial dilator responsiveness in accounting for the decrease in cardiovascular events reported in large multicenter clinical trials, including reduced vascular inflammation that in turn might stabilize atherosclerotic plaques. In this regard, Ridker et al reported that reduction in cardiovascular risk with pravastatin was apparent in CARE trial participants with the highest levels of C-reactive protein and serum amyloid A but not in those with the lowest levels of these serum markers of inflammation. Furthermore, statin therapy, but not placebo, lowered levels of C-reactive protein over the course of this study. These observations raise the possibility that surrogates other than endothelial vasodilator function testing may be more informative in predicting risk reduction not only for statins but for other therapies under consideration for halting the progression and clinical expression of atherosclerosis.

References

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