Editorial

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 constrictor 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.
in the Atorvastatin Versus Revascularization Treatment (AVERT) trial.\textsuperscript{12} Second, longer duration of therapy might have shown beneficial effects, although Treasure (one of the investigators in CARATS) et al\textsuperscript{b} found 5.5 months of statin therapy sufficient to reduce coronary artery constrictor responses to acetylcholine that were significantly different from responses of placebo-treated patients, with pretreatment LDL cholesterol levels in this study population only 10% higher than those in the CARATS cohort. Third, patients in CARATS randomized to placebo showed improved epicardial coronary responses to acetylcholine and to substance P at 6 months, consistent with improved endothelial function in this group over time. This might have been due to greater use of medications shown to improve endothelial vasodilator function (ACE inhibitors, estrogen, and antioxidant vitamins used by 11 patients in the placebo group versus 6 patients in the simvastatin group), although the endothelial effects of these medications might have been present at baseline as well as after 6 months of placebo treatment. Finally, the study might have been underpowered to show benefit of therapy, although more patients participated in CARATS than in the previously published studies of effects of statin therapy on coronary endothelial vasodilator function.

Despite these concerns regarding interpretation of the CARATS study, a reasonable conclusion is that statin lipid-lowering therapy does not invariably improve coronary endothelial function, at least with respect to agonist-induced release of dilator substances, including nitric oxide. Unknown from all reported studies of effects of statin therapy on endothelial function is whether improved dilator responsiveness to acetylcholine (or any other endothelium-dependent dilator agonist) or to shear stress (flow-mediated dilation) predicts prevention of myocardial ischemia or reduction in cardiovascular morbidity and mortality risk. Since cardiovascular risk was not eliminated with statin therapy in clinical trials, it is possible that those patients who suffered cardiovascular end points despite statin therapy did not have improved endothelial vasodilator function and vice versa. Such a study would be difficult to perform because of the large numbers of endothelial function studies required, given the relatively low number of events in patients with stable coronary artery disease appropriately managed with medications and, in a subset, revascularization.

However, several studies suggest that therapeutic improvement in endothelial vasodilator function of patients with coronary artery disease does not necessarily translate into reduced ischemia or lower risk of cardiovascular events, thus questioning the relevance of improved endothelial vasodilator function as a mechanism for therapeutic benefit of statin therapy. In this regard, discussions are provided for 4 therapies that have been shown to improve endothelial vasodilator function in humans, but with unclear relevance for prevention of ischemia or reduction in cardiovascular risk.

**ACE Inhibitor Therapy**

ACE inhibitor therapy has been shown in several studies to improve endothelial vasodilator function in the coronary and systemic circulations of patients with coronary artery disease, potentially through increased bradykinin bioactivity and stimulation of B\textsubscript{2}-kinin receptors on the endothelium, resulting in increased nitric oxide synthesis and release. However, 1 year of double-blind treatment with captopril produced no difference in exercise capacity or the frequency of ST-segment depression despite significant reduction in frequency of cardiovascular events compared with placebo-treated patients in the Captopril And Thrombolysis Study (CATS) of 244 postinfarct patients.\textsuperscript{13} Accordingly, vascular effects of ACE inhibitor therapy that are not testable by studies of endothelial vasodilator function, including enhanced fibrinolysis and protection of vulnerable plaques from rupture due to diminished inflammation, may be of greater importance in accounting for reduction in risk of cardiovascular events.

**Hormone Replacement Therapy**

Estrogen therapy has been shown by several groups to improve endothelium-dependent vasodilation of coronary and systemic arteries in postmenopausal women, including those with coronary artery disease, by enhancing nitric oxide bioactivity. However, effects of estrogen on exercise-induced ischemia in women with coronary artery disease in randomized, double-blind, placebo-controlled trials have been conflicting.\textsuperscript{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.\textsuperscript{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 (e.g., 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),\textsuperscript{17} other clinical trials, including the GISSI-Prevenzione\textsuperscript{18} and the Heart Outcomes Prevention Evaluation (HOPE) trials,\textsuperscript{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 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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