Some of the treatments we use in cardiology must be applied urgently, such as cardiopulmonary resuscitation or thrombolytic therapy for myocardial infarction. The urgency is driven by pathophysiological imperatives, such as the need to prevent cerebral anoxia or to limit the extent of myocardial necrosis. Most other therapies can be instituted in a more leisurely way. Cholesterol lowering is often the last thing that we do, the treatment that we are slowest to initiate.

See p 3227

One of the reasons is that cholesterol levels are depressed for several weeks after the onset of an acute coronary event, and some of us wait to obtain measurements. Some of us withhold drug therapy in coronary patients to see whether diet alone will be effective, even though most coronary patients will not meet the LDL cholesterol goal of 100 mg/dL with diet alone. Also, we have understood that cholesterol lowering appears to reduce coronary events only after a delay. The outcome curves of the secondary prevention trials do not separate appreciably until 1 to 2 years after initiation of treatment.

Several pieces of accumulating evidence, including the article by Dupuis et al in this issue of Circulation, indicate that we may have to reassess our approach. These investigators have demonstrated in patients with unstable angina that cholesterol lowering with pravastatin improved endothelial function within 6 weeks. If cholesterol lowering has relatively immediate consequences that may favorably affect coronary events, the benefits of cholesterol lowering could be extended to acute coronary conditions, and the speed with which we initiate this form of treatment would have to increase dramatically.

Mechanisms Accounting for Long-Term Benefit

Unstable angina and myocardial infarction are caused by abrupt progression of coronary disease, usually due to thrombus formation on a ruptured or eroded plaque. Plaque ruptures occur frequently among patients with coronary disease. Most plaque ruptures do not precipitate coronary events, but rupture with subsequent healing of the plaque is probably a more important mechanism of progression than the slow accretion of lipids and cellular components into the plaque.

Studies in nonhuman primates and extrapolations from autopsy data indicate that cholesterol lowering reduces foam cell and cholesterol ester content of plaques and increases fibrosis. These changes occur slowly, over months to years, and produce a stable plaque that is resistant to rupture. Lower blood cholesterol levels lead to reduced cholesterol uptake by the arterial wall, so that the intrinsic antioxidant properties of the wall are less likely to be overwhelmed, inflammation is reduced, and the slow type of progression due to plaque accretion is retarded.

Coronary angiographic trials have consistently documented that cholesterol lowering slows the progression of coronary atherosclerosis. The average changes in coronary arterial dimensions in these studies are small, because most lesions do not change during the 1- to 5-year course of an angiographic trial and because up to 10 to 15 lesions are measured per patient, so that the lesions that progress are diluted out by those that do not. Small differences in measured dimensions are sufficient to account for the large percentage reductions in coronary events, because the events are due to plaque rupture of a relatively small number of lesions.

Potential Mechanisms Accounting for Short-Term Benefit: The Wall

Several studies have shown that cholesterol lowering improves endothelial function, measured either as brachial artery flow-mediated vasodilation or as acetylcholine-induced coronary vasomotion. Tamai et al recently reported that in a series of 7 patients, 5 of whom had documented coronary disease, endothelial function improved immediately after a single session of LDL apheresis. This was accompanied by an increase in the local production of NO metabolites. The plasma levels of total and oxidized LDL cholesterol correlated with the degree of improvement, as did the level of NO metabolites.

The relevance of this study to clinical practice is open to question, because short-term changes in LDL cholesterol of this magnitude (from a mean of 142 to 33 mg/dL) are not seen with standard care. Nevertheless, O’Driscoll et al showed that simvastatin improves endothelial function within 4 weeks, albeit mainly in subjects without documented atherosclerosis. In this issue, Dupuis et al show that 6 weeks of pravastatin therapy improved flow-mediated endothelium-dependent vasodilation of the brachial artery in patients with unstable angina and myocardial infarction. On the basis of previous studies, these results are not surprising; however,
because of the multifaceted role that endothelial dysfunction plays in acute coronary syndromes, these findings may have therapeutic implications.

The balance between thrombus formation and spontaneous thrombolysis appears to be crucial to the clinical outcome in acute coronary syndromes. A decrease in NO resulting from endothelial dysfunction increases thrombogenicity by several pathways: increased platelet adhesion, inhibition of plasminogen activator and stimulation of plasminogen activator inhibitor, induction of the procoagulant tissue factor mRNA, inhibition of mRNA transcription of thrombomodulin, and stereochemical alterations in heparan sulfate proteoglycans.10

Inflammation in coronary plaques is inhibited by NO at several points.10,11 In patients with unstable angina, persistent elevation of C-reactive protein levels, an indicator of ongoing inflammation, predicts recurrent instability.12 Healthy endothelium modulates coronary tone through the actions of NO on vascular smooth muscle in the media. Even when the intima is thickened by atherosclerosis, improvements in endothelial function by cholesterol lowering can improve NO-mediated vasodilation.13

**Potential Mechanisms Accounting for Short-Term Benefit: The Platelet**

In an ex vivo flow chamber system that simulates plaque rupture, platelet thrombus deposition was higher in coronary patients with hypercholesterolemia than in control coronary patients with normal cholesterol levels.14 After 2.5 months of pravastatin therapy, platelet thrombus deposition was significantly reduced in the hypercholesterolemic group, to a level similar to that of the control patients.14 Nofer et al15 demonstrated that LDL cholesterol inhibits the Na+/H+ antiport on the cholesterol membrane to prevent it from counteracting the intracellular acidification that is associated with platelet activation. Platelet reactivity to activating stimuli is thereby augmented.

Lowering LDL cholesterol with apheresis increased Na+/H+ antiport activity and intracellular pH in patients with familial hypercholesterolemia.15

Platelets and endothelium interact in a variety of ways when healthy or dysfunctional, such that harmful or beneficial effects on both systems are magnified by the interaction. Although it is often difficult or impossible to determine the clinical relevance of isolated mechanisms observed in experimental models, hypercholesterolemia and cholesterol lowering appear to be important factors in acute coronary syndromes.

**Clinical Trials**

No clinical trial data are currently available to determine whether or not the potential benefits described above will translate into a reduction in events in patients with acute coronary syndromes. Unstable angina and recent infarction (within 3 or 6 months) were exclusion criteria in the 3 large secondary prevention trials with statins. Starting cholesterol-lowering therapy at the time of an acute coronary syndrome can now be justified, but only on the basis of the clear, long-term benefit documented in stable coronary patients.

Can improvements in endothelial function be used as a surrogate for coronary event reduction? This surrogate has recently failed quite miserably. Hormone replacement therapy improves endothelial function in postmenopausal women16–18 with coronary disease17 and even ameliorates markers of fibrinolysis and inflammation,18 but it did not reduce coronary events in the only controlled, secondary prevention trial in which it has been tested.19 Too many unappreciated factors may be influencing outcomes, so that endothelial function is not a reliable substitute for clinical end points.

Could aggressive cholesterol lowering be harmful in patients with unstable angina or myocardial infarction? Two pieces of weak, circumstantial evidence can be mustered to support this hypothesis. After cessation of an atherogenic diet in nonhuman primates, the early phase of regression features the precipitation of cholesterol monohydrate and apparent worsening of lesions.3 The failure of secondary prevention trials of cholesterol lowering to show a reduction in events during the first 2 years contradicts the pattern in the primary prevention trials and could conceivably be due to an early competing harmful effect.

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial is currently randomizing 3000 patients with unstable angina or non-Q-wave myocardial infarction to atorvastatin 80 mg/d or placebo, beginning within 1 to 4 days of hospitalization and continuing for 16 weeks of follow-up.20 The primary outcome measure is the time to occurrence of an ischemic event, defined as death, nonfatal myocardial infarction, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia with emergency rehospitalization. Recruitment for MIRACL will be completed in 1999, and the results should be reported next year. Another trial currently in the final stages of protocol development will test the effects of early versus delayed simvastatin therapy in 4500 patients with acute coronary syndromes followed up for 1 year.

These studies should define whether or not acute cholesterol lowering should play a role in patients with unstable angina and myocardial infarction and fill the loophole that now exists between primary and secondary prevention. Soon cholesterol lowering may no longer be the last thing that we do. Imagine, some day we may even find ourselves in the Emergency Department, pushing an IV bolus of a statin. Who knows? Stranger things have happened!

**References**


**KEY WORDS:** Editorials ■ cholesterol
Cholesterol Lowering: Should It Continue to Be the Last Thing We Do?

David Waters

Circulation. 1999;99:3215-3217
doi: 10.1161/01.CIR.99.25.3215
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/99/25/3215

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/