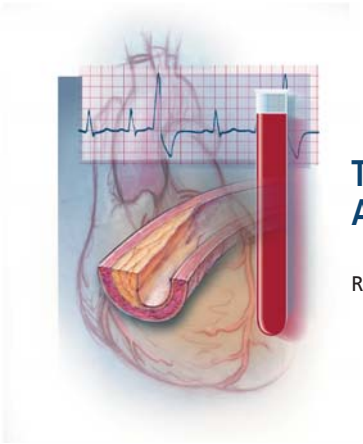

The new "lower is better" lipid goals: Are they achievable with today's drugs?

ROBERT J. CHILTON, DO

Both the newly revised Adult Treatment Panel (ATP III) guidelines developed by the National Cholesterol Education Program and prospective trials indicate that lowering serum low-density lipoprotein cholesterol (LDL-C) to levels of less than 100 mg/dL is beneficial to minimize the risk of coronary heart disease (CHD). However, the risk of acute coronary events is related not just to lipid levels, but also to inflammatory pathophysiologic processes that heighten the risk of plaque rupture. Statin therapy effectively lowers LDL-C to target (optimal) levels, and the newer formulas are proving to provide greater reductions. In addition, research demonstrates that statins also counteract thrombosis, reduce inflammation, improve endothelial function, block plaque formation and progression, and stimulate the growth of new blood vessels in ischemic tissues. Global risk reduction—including diet, exercise, weight loss, and drug therapy are keys to minimizing CHD events.

(Key words: endothelial function, fibrous cap, global risk reduction, low-density lipoprotein cholesterol [LDL-C], plaque rupture, stable plaque, statins, thrombosis)

Although lowering elevated serum cholesterol levels is widely recognized as the key to protection against coronary heart disease (CHD), the debate continues about which lipid levels are optimal for preventing coronary events. The Atherosclerosis Risk in Communities (ARIC) study,[1] in which more than 12,000 middle-aged subjects with no evidence of CHD were followed up prospectively for 10 years, answers this question. Outcomes were measured in terms of CHD-related death, myocardial infarction (MI), silent infarction, coronary artery bypass graft, and angioplasty. The incidence of these CHD events was lowest in the subjects with baseline serum low-density lipoprotein cholesterol (LDL-C) levels of less than 88 mg/dL for women and less than 95 mg/dL for men, whereas the relative risk was nearly tripled in the subjects with the highest LDL-C levels.

The ARIC study, which can be thought of as "the Framingham of the future," confirms the wisdom of the new Adult Treatment Panel (ATP III) guidelines developed by the National Cholesterol Education Program, which identify LDL-C levels of less than 100 mg/dL as optimal and emphasize the value of aggressive, multifactorial risk reduction for primary CHD prevention.[2]

Vascular biology: Pathogenesis of acute coronary syndromes

During the past decade, it has become increasingly clear that thrombosis is the cause of most acute complications of atherosclerosis (particularly unstable angina and acute MI) and that the pathophysiology of these events is deeply rooted in inflammatory processes. Most coronary thromboses begin with a rupture of the protective fibrous cap overlying the plaque (*Figure*).[3-7] The biomechanical strength of this cap is strongly influenced by inflammatory mediators: for example, enzymes that degrade the integrity of the fibrous cap, such as matrix metalloproteinases, are induced by proinflammatory cytokines.[8-11]

Inflammatory processes can also cause the death of smooth muscle cells, which are essential to preventing thrombosis because they repair and maintain the collagenous matrix of the fibrous cap and produce extracellular matrix macromolecules in the arterial wall. Sites of fatal thrombosis due to plaque rupture usually have few smooth muscle cells. Inflammatory mediators may also be lethal to endothelial cells, a process that can occasionally cause thrombosis in coronary arteries due to superficial erosion of the intima without rupture of the fibrous cap. In other circumstances, inflammatory mediators cause endothelial cells to release tissue factor, a potent procoagulant. Last, inflammation may hinder arterial blood flow by impairing the vasodilator function of endothelial cells. In conclusion, inflammatory processes are a major determinant of the acute thrombotic events underlying CHD.[3,6,12,13]

Aggressive treatment of cardiovascular risk factors

There is no dispute about the ability of lipid lowering to reduce coronary events and stroke, yet these effects are often achieved without substantial decreases in vascular stenosis, which suggests that lipid lowering may produce *qualitative* changes in the plaque via anti-inflammatory effects. Preliminary findings now confirm that lipid lowering reduces inflammatory cells and mediators, depresses the levels of matrix metalloproteinases and tissue factor, increases interstitial collagen content, and promotes maturation of smooth muscle.[14-17] The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in particular are now known to do much more than lower cholesterol levels: they also

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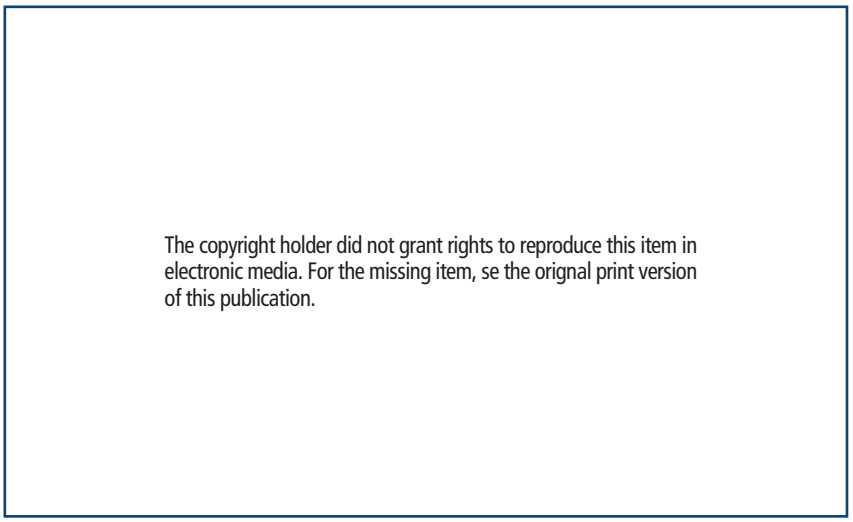

Figure. *Initiation, progression, and complication of human coronary atherosclerotic plaque.* Top: *Longitudinal section of artery depicting "time-line" of human atherogenesis from normal artery (1) to atheroma that caused clinical manifestations by thrombosis or stenosis (5, 6, 7).* Bottom: Cross sections of artery during various stages of atheroma evolution. Normal artery (1); *lesion initiation (2); evolution to fibrofatty stage (3); progression of lesion (4); rupture of fibrous cap (5); resorption of thrombus (6); occlusive thrombus (7). (Reprinted with permission from Libby P. Current concepts of the pathogenesis of the acute coronary syndromes.* Circulation. *2001;104:365-372.)*

have plaque-stabilizing properties, beneficial effects on endothelial function and fibrinolysis, and antithrombotic qualities.[18] These changes can be expected to produce more stable plaques that are less likely to cause thrombosis even if they do rupture.[13]

Antithrombotic effects

Three months of treatment with simvastatin (20 mg/d) has been shown to significantly slow clotting time in patients with advanced CHD and hypercholesterolemia by interfering with prothrombin activation ($P=.004$), heavy-chain factor Va generation ($P=.007$), factor XIII activation ($P=.001$), and fibrinogen cleavage ($P=.002$), as well as promoting light-chain factor Va inactivation ($P=.02$). These effects are unrelated to the drug's effects on cholesterol levels.[19] Both simvastatin and fluvastatin sodium inhibit tissue factor in macrophages (although pravastatin sodium does not). Because tissue factor is an important initiator of coagulation, this may be one mechanism by which statins prevent thrombotic events.[13,20] Statins have been reported to improve cerebral blood flow and reduce stroke size in mice.[21]

Endothelial benefits

The positive effects of statins on endothelial function produce dramatic increases in blood flow to the heart.[22] Automated quantitative analysis of positron emission tomography scans of the hearts of two patients with CHD showed the size and severity of myocardial perfusion abnormalities after dipyridamole-induced stress. At baseline, both patients showed severely limited blood flow, a characteristic of coronary atherosclerosis that is attributable to microcirculatory endothelial dysfunction.[23] One patient was treated with strict dietary restrictions plus statin and resin therapy to achieve acute cholesterol lowering, while the other patient received antianginal therapy alone.

After 90 days, the patient treated with lipid-lowering therapy showed marked regression of the myocardial perfusion abnormalities, whereas the patient treated with antianginal therapy alone actually showed progression. The first patient's gain in coronary blood flow reflects improvement in endothelial cell function, since atherosclerosis does not regress in as short a period as 90 days. In fact, the size and severity of the perfusion abnormalities returned to baseline levels within 60 days of discontinuing the lipid-lowering treatment, supporting the idea that the benefits are due to changes in vasomotor function related to endothelial healing, rather than anatomic changes in the degree of stenosis.[23,24]

Recent data suggest that statins may even be able to stimulate the growth of new blood vessels (neovascularization) in ischemic zones of heart disease. Vasculogenesis in ischemic tissue depends on the mobilization of circulating, bone-marrow-derived endothelial progenitor cells, which differentiate in situ into endothelial cells. In a study of 15 patients with CHD, just 28 days of atorvastatin calcium therapy more than quadrupled the number of these cells ($P<.05$) and enhanced their migratory capacity. Therapeutic neovascularization may become an important strategy for salvaging tissue after ischemic injury.[25]

Anti-inflammatory effects

A possible anti-inflammatory property that may contribute to prevention of CHD is activation of the nuclear receptor peroxisomal proliferation activating receptor-α (PPAR-α). This receptor regulates the expression of several genes implicated in atherogenesis and plaque stability. Agonism by PPAR-α can curb cytokine-induced activation of inflammatory processes in vascular endothelial cells.[13] Fatty acids are among the natural ligands for PPARs, and PPAR-α plays a central role in fatty acid metabolism. In addition to reducing LDL-C levels, statins also increase the levels of serum high-density lipoprotein cholesterol (HDL-C) and its major apolipoprotein apo A-I, which are antiatherogenic and protect against development of CHD. Recent evidence suggests that both this antiatherogenic effect and the anti-inflammatory effects are mediated via PPAR-α,[26] meaning that statins benefit patients by various mechanisms in addition to lowering LDL-C levels.

New technologies for identifying vulnerable plaques

The degree of calcification of atherosclerotic plaques was once thought to predict the likelihood of rupture, because calcium is stiffer and less flexible than the

Table 1
Long-term Efficacy and Safety of Rosuvastatin Versus Atorvastatin Calcium: Results of a 52-Week Comparator-Controlled Trial (N = 412)

Variable*	Treatment (mean daily dose) Rosuvastatin (9.3 mg)	Rosuvastatin (13.4 mg)	Atorvastatin (20.8 mg)
☐ Reduction in LDL-C, %	47†	53†	44
☐ Reduction in apo B, %	39	43†	38
☐ Reduction in triglycerides, %	20	21	19
☐ Change in HDL-C, %	2	3†	−1
☐ Patients achieving ATP LDL-C goal, %	88	98	87
☐ Patients at high risk for cardiac events achieving ATP LDL-C goal, %	65	97	61

*Change from baseline in lipid values after 1 year of treatment with rosuvastatin or atorvastatin. LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ATP, Adult Treatment Panel.

†$P<.05$ versus atorvastatin.

Source: Olsson A, Southworth H, Wilpshaar JW. Long-term efficacy and safety of rosuvastatin: results of a 52-week comparator-controlled trial versus atorvastatin. *Eur Heart J*. 2001;22(suppl):253; abstract 1410.

other components of the plaque. However, a recent study using intravascular ultrasound (IVUS) suggests exactly the opposite: coronary artery calcification is greatest in the culprit stenoses of patients with stable angina, less in patients with unstable angina, and even less in patients with acute MI. This suggests that calcium actually contributes to plaque stability, which has important implications for methods that identify coronary stenoses by relying on the presence of calcium.[27]

A recently developed molecular imaging agent that specifically targets fibrin now permits the visualization of thrombi within fissures of vulnerable atherosclerotic plaques. This technology may be used in the future to identify "hot" plaques (those likely to rupture), which may facilitate early treatment decisions.[28]

Clinical implications

The effects of statins on the pathophysiologic processes of CHD have clear clinical correlates. A recent IVUS study measured intracoronary plaque volume and echogenicity in 131 patients treated with atorvastatin or a mix of other lipid-lowering drugs for 1 year after an intracoronary revascularization procedure.[29] Echogenicity is a measure of plaque composition, with hyperechogenic plaque having a larger fraction of microcalcifications and dense fibrous or elastic tissue, and hypoechogenic plaque having a larger fraction of loose fibrous, lipid, necrotic, or thrombotic tissue.[29]

Atorvastatin reduced mean LDL-C levels by 42%, to an endpoint mean value of 86 mg/dL, whereas the other drugs reduced LDL-C levels by only 16%, to 140 mg/dL ($P<.0001$). Mean absolute plaque volume rose 2.5% in the group treated with atorvastatin, compared with 11.8% in the group treated with the mix of other lipid-lowering drugs, although this difference was not statistically significant. However, plaque hyperechogenicity increased by 42.2% in the atorvastatin-treated group, compared with just 10.1% in the group treated with the other drugs, a significant difference ($P=.021$). This increase suggests that the plaque in the coronary artery wall became stiffer during the course of statin therapy as a result of a change in its composition, making it unlikely to rupture as easily. In fact, the number of ischemic events was lower with atorvastatin than with the other drugs (14 vs 21 events), although the difference was not significant.[29]

In addition to their ability to stabilize atherosclerotic plaques, statins can significantly shrink them over the long term. In a recent study of 18 asymptomatic hypercholesterolemic patients,[30] magnetic resonance imaging was used to visualize plaques in the aorta and coronary artery at baseline and after 1 year of treatment with simvastatin. The drug produced significant decreases in serum total cholesterol and LDL-C ($P<.01$), and significant increases in HDL-C ($P<.01$) within 6 weeks, which were sustained throughout the study. At 12 months, both the aorta and carotid artery plaques showed significant decreases in maximal vessel wall thickness ($P<.001$ and $P=.005$, respectively) and vessel wall area ($P<.001$ and $P<.001$, respectively), a surrogate measure of atherosclerotic burden. The decrease in lesion size without change in lumen size (inward remodeling) probably reflects depletion of lipid content, which indicates structural changes favoring plaque stabilization.[30] A separate study confirmed these findings in patients treated with niacin, lovastatin, and colestipol hydrochloride for 10 years.[31]

Future considerations

The numerous benefits of statins on the pathobiology of CHD and clinical outcomes ensure that they will continue to be a central component of preventive therapy. Statins that are now in development appear to be even more potent than existing members of the class, and are therefore likely to help more patients meet the new ATP III lipid targets. Rosuvastatin, for example, was recently evaluated in a long-term study of more than 400 hypercholesterolemic patients.[32] The subjects were randomly assigned to receive rosuvastatin, 5 mg or 10 mg, or atorvastatin calcium, 10 mg, as a starting dose. During the 40-week dose-titration period, doses could be sequentially doubled to meet LDL-C goals. Rosuvastatin produced statistically significantly greater reductions in LDL-C than did atorva-

Table 2
Long-Term Efficacy and Safety of Rosuvastatin Versus Pravastatin Sodium and Simvastatin: Results of a 52-Week Comparator-Controlled Trial (N = 477)

Variable*	Treatment (mean daily dose)			
	Rosuvastatin (9.5 mg)	Rosuvastatin (13.8 mg)	Pravastatin (32.6 mg)	Simvastatin (36.3 mg)
☐ Reduction in LDL-C, %	42†	48†‡	32	38
☐ Reduction in apo B, %	35†‡	39†‡	25	31
☐ Reduction in triglycerides, %	16	18†	9	14
☐ Increase in HDL-C, %	4	8	4	6
☐ Patients achieving LDL-C goal, %	88	88	60	73
☐ Patients at high risk for cardiac events achieving LDL-C goal, %	84	71	6	30

*Change from baseline in lipid values after 1 year of treatment with rosuvastatin, pravastatin, or simvastatin in 477 hypercholesterolemic patients. LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

†$P<.05$ versus pravastatin.

‡$P<.05$ versus simvastatin.

Source: Brown WV, Zedler BK, Bays HE, Hassman HA, Chitra RR. Long-term efficacy and safey of rosuvastatin: results of a 52-week comparator-controlled trial versus pravastatin and simvastatin. *Eur Heart J.* 2001;22(suppl): abstract 1526.

statin at weeks 12 and 52 ($P<.05$) (*Table 1*).[32] In the atorvastatin-treated group, 87% of patients met the LDL-C goals specified by the ATP III guidelines. In comparison, 98% of the patients randomly assigned to receive the 10-mg dose of rosuvastatin met these targets, including 97% of those in the high-risk category (ie, those with CHD, peripheral vascular disease, or diabetes).[32]

In a similar study, rosuvastatin at doses of 5 mg and 10 mg was compared with pravastatin sodium, 20 mg, and simvastatin, 20 mg, in 477 hypercholesterolemic subjects.[33] During the 40-week dose-titration period, doses could be sequentially doubled to meet LDL-C goals. After 52 weeks of treatment, rosuvastatin caused great reductions in LDL-C levels (42% for the 5-mg dose and 48% for the 10-mg dose). Of all the treatment arms, the 10-mg dose of rosuvastatin produced the greatest effect on LDL-C, HDL-C, and triglyceride levels, and both doses brought 88% of patients to their LDL-C target specified by the ATP III guidelines. Among patients at high risk for CHD, rosuvastatin enabled 71% to 84% to reach this goal, compared with just 6% of the high-risk pravastatin-treated patients and 30% of the high-risk simvastatin-treated patients (*Table 2*).[33]

These two studies demonstrate that rosuvastatin treatment resulted in greater reductions in LDL-C than did atorvastatin, pravastatin, and simvastatin, allowing more patients to meet their lipid goals.[32,33] The results show rosuvastatin to be a credible alternative for treating patients with hypercholesterolemia.

Ongoing trials will help to elucidate the benefits of various forms of treatment. Among the most important of these is the Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial. This randomized multicenter study is currently examining the effects of aggressive (ie, LDL-C goal of 60 mg/dL to 80 mg/dL) medical management with or without interventional revascularization procedures on all-cause mortality and nonfatal MIs in patients with CHD, angina, prior MI, or myocardial ischemia, with reversible defects. Patients at high risk for CHD events are excluded. More than 3000 subjects have already been enrolled, making this one of the largest studies of its kind. Maximal medical treatment consists of amlodipine besylate, simvastatin, fosinopril sodium, metoprolol succinate, aspirin, and modification of maximal risk factor. Preliminary data from the ongoing COURAGE trial appear to show that maximal medical treatment of patients to low LDL-C levels is successful.

Comment

Global risk reduction does more to prevent CHD events than reduction of any one single risk factor. For patients with existing CHD or CHD risk equivalents, such as diabetes, the ATP III guidelines recommend an LDL-C goal of less than 100 mg/dL, and this goal is eminently achievable with a multifactorial approach that includes diet, exercise, and drug therapy. The newer statins offer particular promise as a way to bring nearly all patients to their target lipid levels. Because a large segment of the US population is at risk for heart disease due to dyslipidemia and other risk factors such as diabetes, normalizing blood lipid levels should vastly reduce the morbidity, mortality, and costs associated with CHD.

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