Cardiovascular disease (CVD) has been the number one cause of death in the United States for more than a century and is projected to remain so for many years to come. In 2003, CVD was the direct cause of 37.3% and a contributing cause in 58% of all US deaths. Of deaths blamed on CVD, 152,000 occurred in people under age 65 years.1

According to the National Health and Nutrition Examination Survey, one in three American adults has some form of CVD. Signs of the disease begin early in life, with one in every six teenagers having evidence of atherosclerosis.2 According to longitudinal data from the Framingham Heart Study, cardiovascular events occur at a rate of 7 per 1000 men aged 35 to 44 years. This number rises to 63 per 1000 for men aged 85 to 94 years. Comparable rates occur for women starting at age 45 years, with the gender gap narrowing with advancing age.3

Role of LDL-C in Atherosclerosis Plaque Formation
Excess cholesterol in the arterial wall is not just a risk factor for atherosclerosis—it is the cause of atherosclerosis,3,4 with low-density lipoprotein cholesterol (LDL-C), or “bad cholesterol,” the primary culprit. Typical LDL-C levels are approximately 30 to 35 mg/dL at birth. By age 20 years, 74% of Americans have LDL-C levels above 100 mg/dL, and 98% have an LDL-C above 70 mg/dL.5

Buildup of atherosclerotic plaque in the arteries begins with endothelial retention of apo B lipoproteins, which include the LDL and very-low-density lipoprotein particles. The concentration of LDL in the endothelium is approximately equivalent to its concentration in serum (1:1 ratio), whereas in other connective tissues, LDL is at a 1:10 ratio vs serum.4 Low-density lipoprotein particles pass in and out of the intima (the inner portion of the endothelial lining), but in excessive quantities, some of the particles tend to become stuck in the endothelial matrix. The first stage of stable lipid accumulation in the vessel, often called fatty streaks, has been observed as early as the teen years.6,7

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Destabilization of Plaque

Stable accumulation of lipids within the blood vessel can progress for many years without producing symptoms. Over the years, the structural makeup of atherosclerotic plaque changes as layers are formed and remodeled. Usually, it is not the plaque blocking the artery that occludes the vessel, but rather the sudden rupture of plaque and acute thrombus formation. For this reason, an acute event (eg, myocardial infarction [MI]) often occurs in the absence of any prior warning signs. Inflammation characterizes all phases of atherosclerosis and is the critical element that connects plaque formation and acute rupture and leads to occlusion and infarction. The five key steps involved in destabilization of plaque are shown in Figure 1.

As LDL-C interacts with cells in the endothelium, its lipids undergo oxidation, which causes the endothelium to fight the foreign invader by attracting a variety of inflammatory cells, including monocytes, from the circulating blood. The monocytes mature into macrophages that engulf or “eat” some of the offending LDL particles. Macrophages filled with LDL tend to appear foamy when viewed under a microscope, hence their description as foam cells. Scavenger receptors (CD36 receptors) on the surface of the foam cells actually attract more of the oxidized LDL particles. The foam cells become enmeshed in the endothelium by the interaction of oxidized LDL.

Over years of gradual buildup, atherosclerotic plaque becomes increasingly unstable and prone to rupture. Plaque that lines the blood vessel eventually develops a layer or “cap” of collagen fibers overlying a soft, unstable lipid core. However, the endothelium attracts other inflammatory cells such as T lymphocytes and mast cells in an attempt to dismantle the fatty buildup in the vessel wall. If the collagen lining cracks under the inflammatory onslaught, blood from the vessel seeps through and interacts with the unstable lipid core, rapidly forming the substances that build a thrombus (Figure 2).

Effect of Reducing LDL-C on Atherosclerotic Plaque

The amount of coronary narrowing from plaque is approximately the same in patients with symptomatic, nonfatal coronary artery disease (eg, angina) as in those who have fatal coronary events. In fact, little difference in quantity of plaque occurs between the asymptomatic state of atherosclerosis and the symptomatic state. This finding suggests that treating patients with atherosclerosis early—before the patient becomes symptomatic—may be the point of greatest impact in preventing future adverse events.

Atherosclerosis can be reversed. Park et al found that cholesterol-filled foam cells trapped at the arterial intima can be remobilized by dynamic exposure to key antioxidants. Several studies have demonstrated that aggressively lowering LDL-C levels significantly reduces atherosclerosis and related clinical outcomes, though the optimal target value for LDL-C remains controversial.

Studies using intravascular ultrasound to measure plaque within the coronary arteries have looked at the effects of cholesterol-reducing medications on the lumen. Nissen and colleagues graphed change in atheroma volume according to mean LDL-C level achieved at follow-up in a number of studies of statin treatment for the secondary prevention of cardiovascular events. Lowering LDL-C levels correlated well with decreased plaque progression, and regression of plaque occurred at LDL-C levels of approximately 75 mg/dL or below. This evidence suggests the value of aggressively lowering LDL-C for secondary prevention of acute coronary syndromes.

The ASTEROID Trial was one of the first to demonstrate clinically significant regression of atherosclerotic plaque with statin treatment using the rigorous measure of percent atheroma volume (PAV). This open-label study evaluated 349 patients requiring coronary angioplasty who received intensive therapy with rosuvastatin calcium 40 mg per day. After 24 months, participants achieved an average LDL-C of 60.8 mg/dL and increased their HDL-C levels by 14.7%. Those with LDL-C lower than 70 mg/dL had a mean change in PAV of -0.98% (P<.001 vs baseline).

The effect of lowering LDL-C levels on secondary prevention of cardiovascular outcomes has been studied in several controlled trials, including the PROVE IT-TIMI 22 substudy, which evaluated the safety of very low serum LDL-C levels achieved through aggressive statin therapy. Following the index event, 1825 patients with acute coronary syndromes were treated either intensively with atorvastatin 80 mg per day or moderately with pravastatin sodium 40 mg per day for 4 months. Patients who achieved the lowest LDL-C levels (<40 mg/dL or between 40-60 mg/dL) had fewer major cardiac events (eg, death, MI, stroke, recurrent ischemia, need for revascularization) than did those with higher LDL-C levels. No statistically or clinically significant differences were seen in any safety parameters (eg, muscle, liver, retinal abnormalities) among those who achieved LDL-C levels of 40 mg/dL or lower, prompting the

Steps in Destabilization of Plaque

1. Endothelial activation
2. LDL entry into blood vessel walls
3. LDL oxidation
4. Breakdown of fibrous cap
5. Thrombus formation

Methods of Plaque Rupture

- Activated macrophages, T lymphocytes, and mast cells at the sites of plaque rupture produce a variety of inflammatory reactions that destabilize lesions
- Inflammation inhibits formation of a stable fibrous cap, attacks collagen in the cap, and initiates thrombus formation


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**Table 1**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Result</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Hazard ratio 0.56; 95% CI, 0.46 to 0.69</td>
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</tr>
<tr>
<td>Secondary</td>
<td>Reduced 47% vs placebo</td>
<td>&lt;.0001</td>
</tr>
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</tr>
<tr>
<td></td>
<td>Reduced 20% vs placebo</td>
<td>.02</td>
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</table>

* Major cardiovascular event was defined as myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.


C-Reactive Protein—Marker of Vascular Inflammation

The results of the JUPITER Trial helped raise awareness of the importance of inflammation in CVD risk, especially among people viewed as low risk for cardiovascular events. Subjects had clinically low LDL coupled with elevated CRP, a known marker of vascular inflammation. The clinical benefit of statins therefore goes beyond reducing the lipids by reducing inflammatory components and stabilizing plaque.

This concept is supported by a study that compared the effects of 3 months’ pretreatment with 40 mg pravastatin or placebo in patients scheduled to undergo carotid endarterectomy. Crisby and colleagues showed that plaque specimens from pretreated patients had significantly lower lipid content but also fewer macrophages, decreased matrix metalloproteinase, and higher collagen content.

Of several inflammatory markers studied in CVD thus far, CRP is the most effective for predicting vascular events. It is preferentially found in diseased vessels but is not present in the normal endothelium. Although CRP correlates only modestly with degree of atherosclerosis, stronger correlations have been shown for the propensity for plaque rupture. Ridker and colleagues retrospectively analyzed the results of four large cohort studies (including the Women’s Health Study and Physicians’ Health Study) that categorized CRP levels lower than 1 mg/L as low risk, 1 to 3 mg/L as intermediate risk, and 3 mg/L or higher as high risk. In the four large-scale studies examined, higher CRP represented an increased risk for a myocardial event.

In a large primary prevention trial known as the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), my colleagues and I examined how reducing LDL-C affected clinical outcomes among more than 6000 low-risk patients. In this study, treatment with lovastatin (20-40 mg/day) significantly reduced the incidence of first acute major coronary events (relative risk 0.63, *P* <.001) and other secondary cardiovascular outcomes. In a further analysis of AFCAPS/TexCAPS data, we stratified the results according to whether subjects had high or low baseline CRP and LDL-C. Among the group with high CRP (>1.6 mg/L) but relatively low cholesterol (LDL-C <150 mg/dL), the number needed to treat (NNT) to prevent 1 event over 5 years was just 43. In contrast, the group with both low CRP (<1.6 mg/L) and low LDL had an NNT of nearly 1000 (Table 2). Because treatment with a statin influenced outcomes in patients with either elevated LDL or elevated CRP, the results suggest a dual goal for statin therapy.

Similar findings were reflected in an analysis of CRP measures from PROVE IT–TIMI 22 data of pravastatin treatment for secondary prevention in acute coronary syndromes. Patients who achieved both low LDL-C (<70 mg/dL) and low CRP (<2 mg/L) on statin therapy had a decreased cumulative incidence of recurrent MI or death from coronary causes. Those who achieved CRP less than 1 mg/L had an even greater benefit. Finally, in an an-

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**Authors**

Although the PROVE IT–TIMI 22 substudy examined LDL-C in a high-risk population of patients with existing acute coronary syndromes, the large-scale JUPITER Trial evaluated lipid lowering in a broader population of healthy people whose LDL-C levels would not normally warrant treatment. Entry criteria for this primary prevention study that enrolled more than 17,800 subjects included LDL-C lower than 130 mg/dL, C-reactive protein (CRP) levels less than 2 mg/L, and no diabetes or prior CVD. In fact, the mean baseline LDL-C of 108 mg/dL was substantially below the level considered appropriate for treatment with statins, particularly in this lower-risk population.

Subjects in the JUPITER trial were initially randomly assigned to receive either rosuvastatin 20 mg per day or placebo for 5 years. However, on the strength of preliminary findings, the independent review board stopped the trial after a median follow-up time of 1.9 years. The primary endpoint to first major cardiovascular event decreased to a highly significant extent (*P* <.00001) among rosuvastatin-treated patients. Treatment with rosuvastatin also significantly reduced the risk of MI, stroke, cardiovascular death, revascularization or hospitalization for unstable angina, and the risk of death from any cause (Table 1).

Mean LDL-C levels at the 1-year follow-up point were reduced from 108 to 55 mg/dL among rosuvastatin-treated subjects, while LDL-C levels remained stable in the placebo group. In addition, 1-year CRP levels dropped from a mean of 4.2 mg/L at baseline to 2.2 mg/L in those who received rosuvastatin.

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ysis based on data from the JUPITER Trial, those who achieved LDL-C levels lower than 70 mg/dL and CRP less than 1 mg/L had a 79% decrease in events in the approximately 2-year study period. Lowering either LDL-C or CRP reduced cardiovascular risk in these studies, but lowering both of these markers yielded superior results.

Conclusion

Atherosclerosis is a multifactorial condition, related not only to excess circulating LDL-C but by inflammation that accelerates lipid accumulation within the vessel wall and induces plaque instability and rupture. Plaque rupture and resulting thrombosis is the primary precipitating event in most acute coronary syndromes. Reducing LDL-C through statin treatment can greatly reduce the risk of CVD events, not only in high-risk patients and those with hyperlipidemia, but also in patients with lower LDL-C levels in seemingly low-risk categories. Reducing elevated CRP with statins prevents cardiovascular outcomes regardless of cholesterol levels but is especially effective when both LDL-C and CRP are reduced. Statin therapy has the potential to reduce plaque destabilization at many levels, not only by removing lipids but also by decreasing the instability of the plaque by modifying the inflammatory cellular process.

References


Table 2

AFCAPS/TexCAPS Results: Number Needed to Treat to Prevent One Cardiovascular Event by Baseline Values

<table>
<thead>
<tr>
<th>Baseline Values</th>
<th>TC/HDL-C, mg/dL</th>
<th>C-Reactive Protein, mg/L</th>
<th>NNT</th>
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<tr>
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<tr>
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<td>62</td>
</tr>
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</table>

Abbreviations: AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; NNT, number needed to treat to prevent 1 cardiovascular event in 5 years.


The American Osteopathic Association has been an active member of the Partnership to Fight Chronic Disease (PFCD) since 2007. The PFCD has been instrumental in raising awareness about rising chronic disease rates in the United States and ensuring that prevention and wellness measures were incorporated into the “Patient Protection and Affordable Care Act” (H.R. 3590), which was recently passed by Congress.

To learn more about the PFCD and how to take action, visit http://www.fightchronicdisease.org/index.cfm.