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LDL-cholesterol and coronary artery disease: where we've been, where we're going

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Introduction

The developed world is experiencing an epidemic of coronary artery disease (CAD). In the United States alone more than 10 million people have symptomatic CAD and approximately 1.5 million people present with new myocardial infarctions yearly, causing 500,000 deaths [1]. The monetary implications of this are staggering, with over 90 billion dollars being spent annually on CAD [1]. As this epidemic has progressed, our understanding of the process of atherosclerosis and CAD has changed and expanded. Paralleling these advances in the pathobiology of atherosclerosis have been data showing that medical treatments effectively diminish the atherosclerotic process. Over the last decade, multiple randomized double blind clinical trials have shown that medical treatment with HMG-CoA reductase inhibitors (statins) significantly lowers LDL-cholesterol and reduces cardiac mortality and morbidity in patients with known CAD and those who are at risk of developing it. The purpose of this article is to review our current understanding of LDL-cholesterol and how it contributes to the development of CAD; how different dyslipidemias affect cardiac risk; and how recently reported clinical trial data suggest that even more aggressive treatment of LDL-cholesterol than recommended by the current National Cholesterol Education Program is indicated for management of patients with CAD and hyperlipidemia.

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Cholesterol and coronary artery disease: from clogged arteries to an inflammatory disease

Acute coronary syndromes (ST segment elevation MI; non-ST segment elevation MI; unstable angina; sudden cardiac death) are diseases which typically develop due to rupture of an atherosclerotic plaque with subsequent thrombus formation in the coronary vasculature [2, 3]. High concentrations of serum cholesterol, particularly LDL-cholesterol, are one of the primary risk factors for developing atherosclerosis. Many in the past have thought that high levels of serum cholesterol contribute to atherosclerosis by accumulating within the arterial wall and that symptomatic coronary disease develops because bulky atherosclerotic plaques progressively enlarge, gradually obstructing the arterial lumen [4]. Over the last two decades, however, additional data indicate that atherosclerosis results from an inflammatory process which involves the endothelium, cytokines, smooth muscle cells, lymphocytes, and tissue macrophages [4–6].

It appears that endothelial dysfunction is one of the earliest pathologic processes in the development of atherosclerosis. Possible causes of endothelial dysfunction leading to atherosclerosis include elevated and modified LDL-cholesterol, free radicals caused by cigarette smoking, hypertension, diabetes mellitus, elevated plasma homocysteine levels, infectious micro-organisms, and genetic factors [4]. Many of these factors are considered traditional "cardiac risk factors". Because of their role in the genesis of atherosclerosis, it may be more appropriate to look at these factors as not just "risk factors" but as atherosclerotic pathogenic factors.

The dysfunctional endothelium elicits several responses which contribute to the atherosclerotic

process. A dysfunctional endothelium is more procoagulant, has an increased adhesiveness to platelets and monocytes, stimulates the migration and proliferation of smooth muscle cells, and has an increased permeability to LDL-particles [4]. LDL-cholesterol not only directly injures the endothelium and underlying smooth muscle cells, but also contributes to the atherosclerotic process by activating other components of the inflammatory process [7]. With increased permeability, the injured endothelium more readily allows LDL-particles to enter the arterial wall in the sub-intimal space [4, 7]. Once in the sub-intimal space, LDL can be minimally modified by oxidation, aggregation, and hydrolysis [4, 7]. This modification process has two stages. First, LDL-particles are minimally modified through the action of resident vascular cells [8]. The minimally modified LDL stimulates the endothelium to express factors such as monocyte chemotactic protein-1 (MCP-1), which attracts monocytes from the arterial vessel lumen into the subendothelial space [9]. Minimally modified LDL also promotes the differentiation of monocytes into macrophages [7] and induces macrophages to release cytokines such as tumor necrosis factor α and interleukin-1, which stimulates the endothelium to express monocyte adhesion molecules [10]. Macrophages in the subintimal space stimulate further peroxidation of LDL producing modified LDL. The fully modified LDL-particles have its protein portion modified such that it is no longer recognized by the LDL receptor and instead is recognized by the macrophage scavenger receptors, which in turn take up the modified LDL [8]. This internalization of LDL leads to the formation of lipid peroxides and facilitates the accumulation of cholesterol esters, resulting in the formation of foam cells [4]. Foam cells release growth factors which induce migration and proliferation of smooth muscle cells [4]. Smooth muscle cells form a fibrous cap over the lipid core. Within this lipid core are lacunae containing smooth muscle cells that produce connective tissue matrix [11]. Hypoxia, cytotoxic peroxidases and possibly apoptosis cause the death of some of the macrophages, resulting in the release of their contents, helping to form a highly thrombogenic lipid rich core [12]. It is the thin capped, lipid rich plaque that is most susceptible to rupture [12]. Thus, LDL-cholesterol not only helps to initiate the inflammatory process of atherosclerosis by causing endothelial dysfunction, but also is instrumental in the continuation of this inflammatory process.

Dyslipidemia and coronary artery disease risk

More than 200 risk factors have been linked to the development of CAD [12]. All risk factors, however, are not created equal. In assessing risk, it is imperative to distinguish between risk factors for which interventions have been proven to lower CAD risk and risk associations based on preliminary or observational data. The 27th Bethesda Conference report classified risk factors based on the strength of evidence that intervention affects CAD outcome [13]. Risk factors for which interventions have been proven effective in lowering cardiac risk include cigarette smoking, hypertension, left ventricular hypertrophy, antithrombotic therapy, high fat and cholesterol diets, and elevated LDL-cholesterol. A second category, risk factors for which interventions are likely to lower risk, includes diabetes mellitus, physical inactivity, reduced HDL-cholesterol, elevated triglycerides, small dense LDL, and post-menopausal state. Other risk factors lack sufficient data showing that interventions which reduce the risk factor lower CAD events independently [13].

Elevated serum cholesterol is an undisputed modifiable risk factor for the development of CAD [14]. Data from the Multiple Risk Factor Intervention Trial (MRFIT) has shown a continuous, graded and curvilinear relationship between elevated cholesterol levels and CAD death rates [14]. Moreover, patients with known CAD have a more significant relationship between elevated LDL-cholesterol and CAD death than do persons without preexisting cardiovascular disease [15]. LDL-cholesterol levels, however, should not be looked at in isolation because an individual's risk of suffering a coronary event is dependent upon the totality of their cardiac risk and abnormalities in their entire lipid panel. For instance, data from the Framingham Heart Study showed that normotensive men, aged 50–70 years with LDL-cholesterol of 100 mg/dl and HDL-cholesterol of 25 mg/dl, had a four-fold increased risk of suffering a coronary event when compared to men with LDL-cholesterol of 220 mg/dl and HDL-cholesterol levels of 85 mg/dl [16]. Individual cardiac risk factors, such as diabetes, hypertension, cigarette smoking, low HDL-cholesterol, high LDL-cholesterol, family history of premature CAD, all increase independently an individual's risk of developing CAD [17].

Diabetes is one of the most potent cardiac risk factors [16, 18]. Haffner et al. showed that patients with type II diabetes who have no previous history of myocardial infarction have the same risk of

Table 1. Coronary heart disease equivalents (clinical conditions which confer a high risk for CHD events)

Coronary heart disease (CHD) equivalents
1. Clinical CHD
2. Diabetes mellitus
3. Symptomatic carotid artery disease
4. Abdominal aortic aneurysm
5. Multiple risk factors conferring a 10-year risk of CHD > 20% *

*Determined from Framingham Risk Model

Adapted from Expert Panel on Detection, Evaluation, Treatment of High Blood Cholesterol in Adults [17].

Table 2. Major risk factors that modify LDL-cholesterol goals

1. Cigarette smoking
2. Hypertension (BP ≥ 140/90 or on antihypertensive medication)
3. Low HDL-cholesterol (< 40 mg/dl)
4. Family history of premature CHD (CHD in male first degree relative < 55 years; CHD in female first degree relative < 65 years)
5. Age (men ≥ 45 years; women ≥ 55 years)

HDL-cholesterol ≥ 60 mg/dl counts as a negative risk factor; its presence removes one risk factor from the total count

Adapted from Expert Panel on Detection, Evaluation, Treatment of High Blood Cholesterol in Adults [17].

suffering a myocardial infarction over a seven-year time period as patients with a previous myocardial infarction who do not have diabetes [19]. For this reason the new ATP III recommendations classify diabetes as a coronary heart disease equivalent. That is to say, patients with diabetes have a similar risk of developing coronary heart disease as do individuals with known CAD. Treatment goals, therefore, for patients with diabetes and no overt coronary heart disease (CHD) should be identical to patients with overt CHD. In both groups LDL-cholesterol should be less than 100 mg/dl (tab. 1) [17, 19].

The presence of multiple concomitant risk factors is of great clinical concern because this tends to increase coronary heart disease risk synergistically [20]. Yusuf et al. assessed the presence of five factors on increasing cardiac risk in 12,932 patients from the NHANES I Follow-up Study [21]. Researchers found that having three risk factors tripled the risk of having a cardiac event while having four or more risk factors increased the cardiac event risk five-fold and the risk for death three-fold [21]. Because risk factors are additive and in some cases interactive, it is important to assess an individual's global cardiac risk. A variety of CAD risk prediction algorithms have been developed which can be used for this purpose [22]. The Framingham Risk Assessment model is one of the most commonly used algorithms and has been incorporated into the new National Cholesterol Education Program's ATP III recommendations [17, 22]. The model is to be used in patients without known CAD and assigns points to specific risk factors. The sum of the points is used to estimate the ten-year risk for developing coronary heart disease. Similar algorithms have been developed for patients with overt coronary artery disease and can be used to estimate the two-year probability of suffering future CAD events [13].

Treating elevated LDL-cholesterol remains the primary target of the new ATP III's guidelines for treating dyslipidemias [17]. Assessing LDL-cholesterol and its associated risk begins with measuring a complete lipid profile, which includes total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. Next, the presence of coronary heart disease or its equivalents (diabetes, symptomatic carotid artery disease, peripheral artery disease, abdominal aortic aneurysm) is identified. The numbers of major cardiac risk factors are then tallied (tab. 2). LDL-cholesterol goals and cut points for lifestyle changes and drug treatment are determined based on the estimated cardiac risk (tab. 3).

Elevated triglyceride levels are also targets for treatment in the new ATP III guidelines. Non HDL-cholesterol, defined as the difference between total cholesterol and HDL-cholesterol, is an indirect measure of the atherogenic, triglyceride rich VLDL particles. Based on the premise that a VLDL-cholesterol ≤ 30 mg/dl is normal, a patient's non-HDL-cholesterol goal is set at 30 mg/dl higher than that for LDL-cholesterol. Because non-HDL-cholesterol contains all of the potentially atherogenic lipid particles, LDL, Lp(a), IDL, VLDL remnants, it may be a more accurate predictor of cardiac disease mortality than LDL-cholesterol [23]. Cui et al. analyzed data from the Lipid Research Clinics Program follow-up study to determine if non-HDL-cholesterol is more useful than LDL-cholesterol in predicting CAD mortality [23]. Researchers studied data from 4,462 men and women with no clinically relevant CAD. The incidence of cardiac death was followed over 19 years. In men, non-HDL-cholesterol and HDL-cholesterol were equally good predictors of cardiac death, while LDL-cholesterol was less predictive. In women, HDL-cholesterol was the

Table 3. LDL-cholesterol goals and cutpoints for treatment according to risk category

Risk category	LDL-cholesterol goal [mg/dl]	LDL-cholesterol level to initiate lifestyle changes [mg/dl]	LDL-cholesterol level to consider drug therapy [mg/dl]
CHD or CHD risk equivalents	< 100	≥ 100	≥ 130 (100–129 — drug therapy optional)
2 + risk factors (10 years risk ≤ 20%)	< 130	≥ 130	10 yr risk 10%–20%: ≥ 130 10 yr risk < 10%: ≥ 160
0–1 risk factor	< 160	≥ 160	≥ 190 (160–189 — drug therapy optional)

Adapted from Expert Panel on Detection, Evaluation, Treatment of High Blood Cholesterol in Adults [17].

best predictor of cardiac death, non-HDL-cholesterol the next best, and LDL-cholesterol the least predictive [23]. Further study is required to more clearly delineate the relative importance of various lipid subfractions in predicting risk.

Elevated LDL-cholesterol is instrumental in the pathogenesis of atherosclerosis. The extent to which elevated LDL-cholesterol confers an increased risk for developing CAD is modified by coexisting risk factors. The remainder of this article will review studies using statins to treat elevated levels of serum LDL-cholesterol.

Cholesterol lowering studies: then and now

Many of the early lipid lowering trials were angiographic studies evaluating the effects of lipid lowering therapy on plaque progression and regression [24, 25]. Lessons learned from these trials include the fact that aggressive cholesterol lowering therapy is effective in arresting or reducing the progression of CAD and that the extent of improvement in the diameter of stenotic lesions is small (1–2%) [24, 25]. These findings suggest that the reductions in cardiovascular events seen in the regression trials may be due to mechanisms independent of anatomic regression.

Subsequent clinical studies with HMG-CoA reductase inhibitors demonstrate that these drugs reduce CAD morbidity and mortality [26–30]. In each of these trials, statin therapy produced a significant reduction in LDL-cholesterol. Some of the beneficial effects of statin therapy may be related to plaque stabilization resulting from regression of lipid rich lesions prone to rupture [31]. Pleiotropic mechanisms by which statins may also act include normalization of dysfunctional endothelium [32], direct anti-ischemic effects [33], and anti-thrombotic actions [34], to mention a few.

To date there have been 5 published, large randomized placebo control trials showing that treating hypercholesterolemic patients with CAD or those at risk for developing it with a HMG-CoA reductase inhibitor significantly reduces future cardiac events (tab. 4).

The Scandinavian Simvastatin Survival Study (4S) examined the effects of simvastatin therapy on overall mortality in patients with known angina or MI. Patients were randomized to simvastatin or placebo and were followed for a mean of 5.4 years [26]. The simvastatin group had a 38% decrease in LDL-cholesterol, a 28% decrease in total cholesterol and an 8% increase in HDL-cholesterol. Compared to the placebo group, the simvastatin group had a 30% reduction in all cause mortality ($p = 0.0003$). Patients treated with simvastatin also had a 37% reduction in revascularization procedures ($p < 0.00001$), 42% reduction in coronary mortality ($p = 0.00001$), and a 34% reduction in major coronary events ($p < 0.00001$). Simvastatin reduced major coronary events in multiple subgroups during post hoc analysis [35, 36]. Of note is the fact that patients with diabetes mellitus treated with simvastatin had the greatest reduction in coronary events (55%) [36].

The average cholesterol of patients in the 4S trial ranged from approximately 200 mg/dl to 300 mg/dl. These cholesterol levels were significantly higher than that of the typical American who suffers an myocardial infarction (MI) [37]. The Cholesterol and Recurrent Events (CARE) study was designed to determine if lipid lowering therapy with pravastatin reduced the incidence of fatal coronary heart disease and nonfatal MI in patients with "normal" cholesterol levels (mean total cholesterol = 209 mg/dl) [27]. A total of 4,159 post MI patients were randomized to pravastatin 40 mg daily or placebo and followed for 5 years. Pravastatin therapy produced a 28% decrease in LDL-cholesterol, re-

Table 4. Major clinical intervention trials of statins

Trial	Prevention	Drug and daily dose	Reduction of LDL-cholesterol	Mortality reduction	Reduction of CAD death
Scandinavian Simvastatin Survival Study [26]	Secondary	Simvastatin 10–40 mg	35%	30%	42%
Cholesterol and Recurrent Events Trial [27]	Secondary	Pravastatin 40 mg	28%	8% (NS)	19%
Long-Term Intervention with Pravastatin in Ischemic Disease [28]	Secondary	Pravastatin 40 mg	25%	22%	24%
West of Scotland Coronary Prevention Study [29]	Primary	Lovastatin 20–40 mg	26%	22% (NS)	33%
Air Force/Texas Coronary Atherosclerosis Prevention Study [30]	Primary	Pravastatin 40 mg	25%	NA	36%

NA — not available, NS — not significant

sulting in a 24% reduction in nonfatal MI or coronary heart disease death ($p = 0.003$)

These data were confirmed in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, in which 9,014 patients with known CAD and total cholesterol levels between 155 and 271 mg/dl were randomized to pravastatin 40 mg daily or placebo [28]. After a 6.1 year follow-up, treatment with pravastatin reduced all cause mortality by 22% ($p < 0.001$), mortality due to CAD by 24% ($p < 0.001$), and stroke by 19% ($p = 0.048$) [28].

The 4S, CARE and LIPID trials showed that statin therapy in patients with CAD and high or average LDL-cholesterol levels significantly reduced mortality and morbidity. The West of Scotland Coronary Prevention Study (WOSCOPS) and the Air Force/ /Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS) examined the effects of statin therapy in primary prevention. In WOSCOPS, 6,595 men with no known history of CAD and mean total cholesterol levels of 272 mg/dl were randomized to pravastatin 40 mg daily or placebo. After 4.9 years of follow-up, nonfatal MI or death from CAD was reduced by 31% ($p < 0.001$) and all cause mortality was non-significantly reduced by 22% ($p = 0.051$) [29]. In AFCAPS/TEXCAPS, 6,605 men and women with no known CAD were randomized to placebo or lovastatin, titrated to achieve an LDL-cholesterol less than 110 mg/dl [30]. After a 5.2 year follow-up, the composite endpoint of fatal or nonfatal MI, sudden death, or unstable angina was reduced by 37% ($p < 0.001$). Of particular interest is that the individuals who benefited most from lovastatin therapy were those with the lowest HDL-cholesterol [30].

The five clinical studies reviewed clearly demonstrate the beneficial effects of statin therapy in primary and secondary prevention of CAD. Several questions relating to treatment goals remain: "How low should an elevated LDL-cholesterol level be reduced?" "Should all individuals with known CAD be started on a statin regardless of their baseline LDL-cholesterol level?" The answer to the first question relates to the mechanism by which cholesterol reduction reduces coronary events. If there is a threshold effect to cholesterol lowering, then LDL-cholesterol levels need only be lowered to below that threshold. Data from CARE suggested that no further risk reduction occurred by lowering LDL-cholesterol below 125 mg/dl [38]. This observation was only noted in the CARE data and likely reflects the population of patients studied. Data from other studies, however, suggest a more curvilinear relationship between reduction of LDL--cholesterol levels and lowering of CAD events [39]. The National Cholesterol Education Program (NCEP) recommends a LDL-cholesterol goal of $\leq$ 100 mg/dl in patients with known CAD (tab. 3) [17]. It is unknown if lowering LDL-cholesterol to levels significantly less than 100 mg/dl will convey added benefit. The ongoing Treating to New Targets (TNT) Study should provide an answer to this question. In this study 8,600 patients with known CAD were randomized to atorvastatin 10 mg/day to maintain an LDL-cholesterol less than 100 mg/dl or to atorvastatin 80 mg/day to maintain an LDL-cholesterol less than 75 mg/dl [40]. The effects of standard care versus aggressive lipid lowering on five-year cardiac event rates will be monitored. Until these data are available, treating to NCEP guidelines is an appropriate starting point. Therapy, however, should be individualized. It is the author's view that extremely high risk individuals may re-

quire more aggressive treatment with a goal of lowering LDL-cholesterol below NCEP guidelines.

Data presented at the November 2001 scientific sessions of American Heart Association provide an answer to the second question, "Should individuals with known CAD be started on a statin regardless of their baseline LDL-cholesterol level?" The recently completed Heart Protection Study is the largest lipid lowering statin study performed to date. In this study 20,536 patients at high risk for coronary heart disease (known MI or CHD, peripheral vascular disease, diabetes mellitus, treated hypertension) were randomized to receive simvastatin 40 mg or placebo. Patients ranged in age from 40–80 years and all had a total cholesterol greater than 135 mg/dl. The primary endpoint was all cause mortality and cardiovascular death. Over the 5.5 year follow-up, treatment with simvastatin compared with placebo significantly reduced all cause and cardiovascular mortality by 12% and 17% respectively [41]. The treatment benefit was seen in all patients regardless of age, sex, and baseline LDL-cholesterol. In fact 33% of patients had baseline LDL-cholesterol levels below 116 mg/dl, 25% were between 116–135 mg/dl, and the remaining 42% had levels greater than 135 mg/dl [41]. These data unequivocally support the idea that statin therapy is appropriate for all patients at high risk for coronary artery disease, irrespective of the baseline LDL-cholesterol level.

Aggressive lipid lowering therapy is an important part of managing the systemic disease of atherosclerosis. Although fine tuning appropriate treatment goals for large populations will continue to occur, an exciting new area in lipid management involves functional determinations of the adequacy of lipid lowering. In this treatment paradigm, non-invasive techniques for assessing arterial health are used to determine the adequacy of lipid lowering treatments. Instead of an absolute LDL-cholesterol level determining the adequacy of lipid lowering therapy, normalization of non-invasive markers of atherosclerotic disease dictates appropriate treatment goals. There are currently three non-invasive imaging methods for assessing arterial health [42]. Carotid ultrasound measurements of intimal medial thickness, brachial artery reactivity testing to assess endothelial function, and magnetic resonance imaging for atherosclerotic plaque characterization have all been proposed as non-invasive measures of arterial health [42]. Though promising, these techniques require standardization of tools, uniformity of operator training, clarification of study populations, and reduction in costs before they will be able to be applied in broad clinical use.

Conclusions

Coronary artery disease is a global disease of epidemic proportions. Elevated serum cholesterol levels play a central role in the genesis of atherosclerotic plaques and aggressive lipid lowering can significantly reduce mortality and morbidity related to CAD. Management of patients with dyslipidemias requires understanding the risk that specific lipoprotein abnormalities convey, identifying coexisting risks, and, as a first step, treating patient's LDL-cholesterol to NCEP goals. Recent data suggest that lipid lowering beyond the ATP III guidelines may be most appropriate. In thinking about dyslipidemia and CAD, it is important to remember that an ounce of prevention is worth a pound of tissue plasminogen activator (t-PA).

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