Lipoproteins, Inflammatory Biomarkers, and Cardiovascular Imaging in the Assessment of Atherosclerotic Disease Activity

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Atherosclerosis is present in about 50% of asymptomatic adults at middle age and in nearly all elderly individuals. The traditional diagnostic and treatment paradigm has addressed risk detection and reduction of binary events, including myocardial infarction (MI), stroke, and cardiovascular death. About 50% of all acute coronary syndromes occur in previously asymptomatic subjects, 90% of whom have modifiable risk factors; yet our current screening approaches fail to prevent the 1.2 million acute cardiovascular events that occur annually in the United States. In a patient with active disease, multiple treatment targets can be approached with a variety of lifestyle changes and medical therapy to render the disease quiescent in theory. A future approach may be interception of atherosclerosis before the identification of theoretical or actual risk of episodic events. This case review highlights use of advanced biomarkers and imaging to assess atherosclerotic disease activity in a 49-year-old asymptomatic woman who presents for evaluation after the death of her father from MI.
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Key words: Coronary artery disease • Biomarkers • Lipoprotein-associated phospholipase A_2 • Cardiac coronary tomography angiography • Cholesterol • Atherosclerosis

The latest figures on all-cause mortality in the United States show that, since 1999, the cardiovascular disease (CVD) age-adjusted death rate has dropped by 25%.[1] With the current trends in obesity and insulin resistance, and the aging of the baby-boomer generation, these rates are likely to reverse. Worldwide, CVD now accounts for more deaths than any other cause of mortality, including infectious disease and other poverty-related

causes. Accordingly, the disease prevalence is expected to continue to rise well beyond the year 2050.[2]

Approximately 50% of all acute coronary syndromes occur in previously asymptomatic subjects, 90% of whom have modifiable risk factors; yet our current screening approaches fail to prevent the 1.2 million acute cardiovascular events that occur annually in the United States.[3] Data from a major international study showed that 9 potentially modifiable risk factors accounted for more than 90% of the risk for CVD. Of these risk factors, levels of proatherogenic lipoproteins in plasma accounted for more than 50% of the population-attributable risk for CVD.[4] These and other data raise awareness of the importance of serum lipoprotein analysis in individuals with atherosclerotic disease activity and identify those with residual CVD risk despite treatment.

New technology is changing our ability to detect and treat subclinical atherosclerosis. Highly accurate imaging modalities, such as multidetector coronary computed tomography angiography (CTA), can expose coronary artery disease (CAD) when it is amenable to pharmacotherapy and lifestyle modification. Furthermore, cholesterol and lipoprotein profiling allows clinical detection of residual risk and CVD in certain individuals. Finally, inflammatory biomarkers, including C-reactive protein (CRP), lipoprotein-associated phospholipase A_2 (Lp-PLA_2), and myeloperoxidase, may provide additional clinical utility beyond traditional methods of calculating current and future risk. This article will describe subclinical atherosclerosis in a woman without traditional risk factors, highlighting the value of cardiovascular imaging and lipoprotein biomarker analysis in identifying atherosclerotic disease activity.

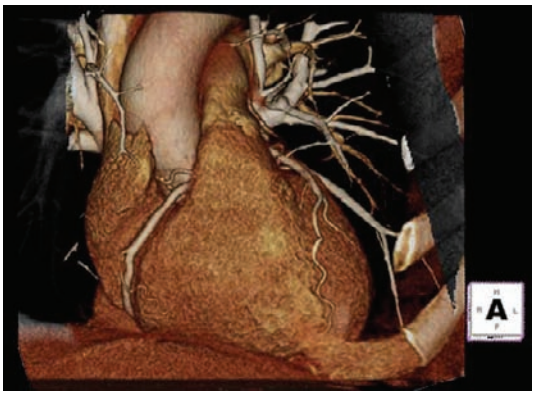

Figure 1. *Volume-rendered computed tomography reconstruction image demonstrating epicardial coronary and great vessels in relation to the bony thorax.*
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Case Report

A 49-year-old attorney was seen in consultation for concerns regarding atherosclerotic risk after the recent death of her father from a myocardial infarction. She had no exertional chest symptoms, claudication, palpitations, or syncope. She did not take medications or supplements and had no other medical problems or family history of premature CAD. The patient led an active lifestyle, did not smoke, and did not use illicit drugs or alcohol.

Her physical examination was unremarkable: weight, 63.0 kg; body mass index, 23.5 kg/m^2; blood pressure, 120/72 mm Hg; and heart rate, 72 beats/min. Laboratory analysis revealed normal blood chemistry, cell counts, and thyroid levels. Total cholesterol was 217 mg/dL, triglycerides were 63 mg/dL, low-density lipoprotein (LDL) cholesterol was 117 mg/dL, high-density lipoprotein cholesterol (HDL) was 67 mg/dL, and non-HDL was 150 mg/dL. The LDL particle number by nuclear magnetic resonance (NMR) spectroscopy (LipoScience™, Inc, Raleigh, NC) was 2148 nmol/L (very high risk $>$ 2000, optimal $<$ 1000 nmol/L), and mean LDL particle size was 20.7 nm. The Lp-PLA_2 level was 314 ng/mL (normal $<$ 200 ng/mL, optimal $<$ 160 ng/mL). The high-sensitivity CRP level was 9.7 mg/L (normal $<$ 1.0 mg/L). The patient underwent CTA, which showed that the proximal segment of the codominant left circumflex had a noncalcified plaque occupying about 20% of the lumen. Similarly, the right coronary artery had a noncalcified plaque occupying 30% to 40% of the lumen in the proximal segment (Figures 1 and 2).

Following the identification of coronary atherosclerosis, this patient was started on aspirin 81 mg/d, rosuvastatin 20 mg/d, and omega-3 fatty acid supplementation (two 1200-mg fish oil capsules for a total of 864 mg of eicosapentaenoic acid and 576 mg of docosahexaenoic acid per day). The patient implemented a moderate-intensity exercise regimen of 30 minutes per day most days of the week and markedly reduced sugar, starches, and saturated fat in her diet. Eight months later, repeat examination revealed that she had lost 5 kg, her Lp-PLA_2 levels had dropped from 314 ng/mL to 141 ng/mL, and her LDL had decreased from 117 mg/dL to 66 mg/dL (Table 1).

Pathophysiology of Atherosclerotic Disease

Atherosclerotic disease behavior can be active or quiescent at various times. These different temporal states vary with gender, age, and risk factors and may be altered by risk factor modification and therapeutic

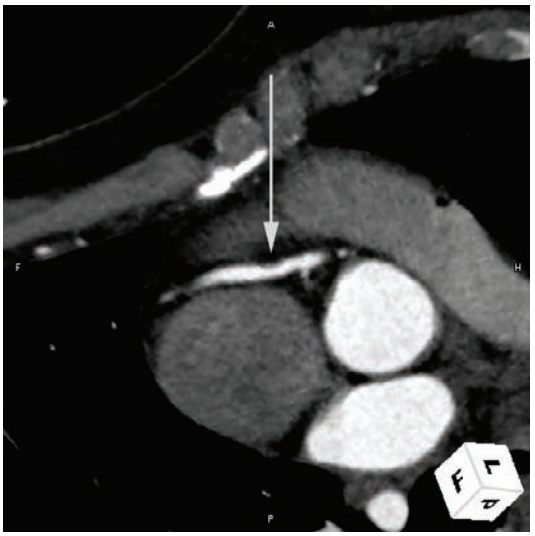

Figure 2. *Curved multiplanar imaging shows lesion in the right coronary artery demonstrated by multidetector row computed tomography (arrow).*
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intervention. Unabated atherosclerotic disease activity results in the clinical manifestations of CAD, stroke, and arterial occlusive disease. The pathophysiology of active atherosclerosis can be divided into 3 components involving dynamic inflammation and deposition of cholesterol, cholesteryl esters, triglycerides, and phospholipids; connective tissue extracellular matrix; and vascular elements, such as smooth muscle cells and inflammatory cells.[5] Various lipoproteins shuttle insoluble cholesterol, cholesteryl esters, and triglyceride compounds to supply cellular elements such as cell walls and other essential metabolic processes.[5] Evolution of atherosclerotic plaques occurs with accumulation of lipoprotein particles that is facilitated by specific lipoprotein receptors in the intima. Over time, oxidation, glycation, and inflammatory processes change plaque composition and lead to fibrosis or ulceration.

Table 1
Patient Characteristics and Laboratory Markers Before and After Lifestyle Changes and Medical Treatment

	Baseline Measurements September 2007	After Lifestyle Changes and Medical Treatment May 2008
Weight (kg)	63	58
Body mass index (kg/m^2)	23.5	21.5
LDL (optimal < 70 mg/dL)	117	66
Non-HDL (optimal < 100 mg/dL)	150	79
HDL (men > 40 mg/dL, women > 60 mg/dL)	67	65
LDL-P number (high risk > 2000 nmol/L, optimal < 1000 nmol/L)	2148	Not measured
Mean LDL-P size (small dense LDL considered ≤ 20.5 nm)	20.7	Not measured
Lp-PLA$_2$ (optimal < 160 ng/mL)	314	141
High-sensitivity C-reactive protein (< 1.0 mg/L)	9.7	Not measured

LDL, low-density lipoprotein; HDL, high-density lipoprotein; LDL-P, low-density lipoprotein particle number; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$.

Atherosclerotic Disease Activity Assessment

It is estimated that by the year 2030, more than 50% of adults older than 40 years will have either the metabolic syndrome or overt diabetes.[2] Despite the bulk of research that supports the central role of LDL in atherogenesis, the cholesterol content of LDL particles varies and is influenced by metabolic abnormalities such as insulin resistance and hyperglycemia.[6] Reduction of elevated LDL cholesterol remains a primary goal in cholesterol screening programs and, once attained, non-HDL concentrations should be given secondary consideration. Despite adequate LDL cholesterol lowering, many individuals (particularly those with insulin resistance) on statin therapy have significant residual risk for CVD. Accordingly, recent consensus guidelines advocate assessment of apolipoprotein B-100 (apoB) or LDL particle number in addition to standard cholesterol panels.[5]

Many large-scale epidemiologic studies of most populations have described a significant dose-response relationship between baseline LDL levels and reduction of LDL using pharmacotherapy and the subsequent risk of CVD.[5] In settings where small, dense atherogenic LDL particles predominate, assessment of apoB provides a more accurate assessment of proatherogenic lipid

burden than general LDL measurements. Furthermore, evaluation of apoB accounts for other atherogenic lipoproteins because each particle of very low-density lipoprotein and intermediate-density lipoprotein also contains 1 apoB molecule.[4] Measurement of apoB levels or direct measurement of the LDL particle number using NMR is a better predictor of disease activity than LDL alone, especially in disease states such as the metabolic syndrome.[6]

ApoB, like LDL cholesterol, is a powerful predictor of risk for future CVD events. One large, multinational prospective study found apoB levels to be the best predictor of risk compared with both traditional risk factors (smoking, physical inactivity, or presence of diabetes) and serum cholesterol concentrations (LDL, non-HDL, triglycerides, or HDL levels).[4] These data are in agreement with prior data from the Framingham Offspring Study, which found apoB to be a more accurate risk factor than total cholesterol or ratios of LDL cholesterol and non-HDL.[7]

The most accurate method of measuring the LDL particle number is with NMR. One analysis of the LDL particle number demonstrated lower residual risk of mortality among patients with a low LDL particle number than correspondingly low (goal) levels of serum LDL concentration.[6] Similarly, LDL particle number measurement by NMR or by indirect assessment by apoB emerges as a superior assessment of the benefits of LDL-lowering therapy than LDL or non-HDL concentrations.[8] However, this approach is limited by expense, test availability, and lack of validation of risk prediction in different ethnicities and ages, and in the presence of other comorbidities that affect lipid metabolism.

Authorities advocate that apoB reduction should be the final test of the adequacy of any LDL cholesterol-lowering regimen.[5] This is because in patients with excess adiposity, cardiometabolic syndrome, and diabetes, or combinations thereof, there is a disconnect between the LDL and apoB levels. Specifically, the LDL can be deceptively low, with measured apoB levels remaining in the elevated range signifying a high number of circulating LDL particles. Based on interpretation of these guidelines, we recommend a tiered approach to lipoprotein screening that includes assessing LDL, non-HDL, and apoB levels. The primary treatment objectives of reducing LDL to goal remain, however, and when apoB levels are more than 10% higher than LDL, then a high prevalence of atherogenic lipoprotein should be suspected and more aggressive treatment should be considered. For example, in someone with an LDL goal of less than 70 mg/dL, an optimal apoB goal should be less than 80 mg/dL (Table 2).

Inflammatory Biomarkers and CVD Risk

The independent and additive value of inflammatory biomarkers for the screening and management of CVD is still under clinical study, and consensus guidelines have not endorsed the potential role of these biomarkers in risk stratification. However, as research in inflammatory biomarkers continues to advance, these may become useful tools for risk stratification or measurement of therapeutic efficacy.

C-Reactive Protein

Associations between plasma levels of CRP and CVD events have driven interest in using this inflammatory biomarker as a marker of risk. CRP is a large pentamer polypeptide produced by hepatocytes in response to interleukin-6, which is an adipokine secreted by intra-abdominal adipocytes. CRP is highly correlated with measures of visceral adiposity, the metabolic syndrome, and excess body fat. Despite this, a major limitation of CRP is lack of specificity in

Table 2
Advanced Stepwise Approach to the Treatment of Atherosclerotic Disease and Reduction in Residual Coronary Risk

Priority Level	Therapeutic Target	Treatment Strategy
1	LDL < 70 mg/dL	Statin, ezetimibe, BAS, niacin
2	Non-HDL < 100 mg/dL	Statin, fibrate, niacin
3	ApoB < 80 mg/dL or LDL-P < 1000 nmol/L	Statin, ezetimibe, BAS, niacin
4	Lp-PLA_2 < 160 ng/mL	Statin, ezetimibe, niacin, fibrate, omega-3 fatty acids
5	Hs-CRP < 1.0 mg/L*	Reduce abdominal adiposity, lipid-lowering therapy, smoking cessation, blood pressure control, glycemic control, other comorbidity reduction

*May not be achievable and not supported by interventional studies or outcome studies at this time.

LDL, low-density lipoprotein; BAS, bile acid sequestrant; HDL, high-density lipoprotein; ApoB, apolipoprotein B; LDL-P, low-density lipoprotein particle number; Lp-PLA_2, lipoprotein-associated phospholipase A_2; Hs-CRP, high-sensitivity C-reactive protein.

the general population. Most elevated CRP levels are due to medical conditions other than atherosclerosis, and the majority of data on CRP are based on retrospective analyses. In most clinical scenarios, the prognostic value of CRP is strongly attenuated by the presence of other coronary risk factors.[9] In contrast to Lp-PLA_2, CRP is not especially useful as an index of coronary heart disease, as it is not secreted by cellular components of atherosclerosis.[10]

The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial demonstrated a reduction in cardiovascular risk in patients with LDL levels of less than 130 mg/dL, but with elevated CRP (> 2.0 mg/L), who were treated with rosuvastatin. Over the 1.9 years of study follow-up, treatment with rosuvastatin decreased the primary composite endpoint by 44% compared with placebo.[10] This study shows that CRP may be useful in the identification of patients in need of treatment with statins, but who are not eligible based on current LDL guidelines.

In another study, CRP polymorphisms were associated with markedly increased CRP levels but not with an increased risk of CAD or ischemic cerebrovascular disease.[11] Thus, the majority of the best evidence suggests that CRP is not pathogenetic, but rather is most appropriately positioned as a marker of cardiometabolic risk related to excess adiposity and may be useful in the identification of patients in need of treatment with statins. Furthermore, interventions that address any 1 of many CVD risk factors are associated with lower CRP values (Table 2).

Lipoprotein-Associated Phospholipase A_2

Lp-PLA_2 is a novel inflammatory marker that may play a key role in the noninvasive assessment of atherosclerotic disease activity in asymptomatic individuals. Unlike CRP, Lp-PLA_2 appears to be pathogenic, as it is produced by macrophages active in the atherosclerotic plaque and promotes atherosclerosis progression by inducing apoptosis of macrophages and smooth muscle cells. Lp-PLA_2 has great affinity for low-density LDL particles, and its enzyme activity cleaves oxidized phospholipids into proinflammatory products: lysophospholipids and fatty acids.[12] Moreover, Lp-PLA_2 is strongly correlated with coronary vascular dysfunction as assessed by the response to intracoronary acetylcholine as opposed to lipoprotein levels.[13] Interestingly, in patients with early coronary atherosclerosis, as determined by intravascular ultrasound, Lp-PLA_2 levels are higher in the coronary sinus than systemic arteries, implying active secretion of Lp-PLA_2 by coronary atherosclerotic elements.[14]

To date, 4 large studies have shown an independent association between Lp-PLA_2 and the risk of future cardiovascular events in candidates for primary prevention.[9,12,15,16] In a series of 580 men with hyperlipidemia (average LDL was 194 ± 17 mg/dL) and no history of CAD, elevated Lp-PLA_2 was associated with an increased risk of coronary events that was not confounded by LDL levels and traditional risk factors despite multivariate adjustments.[9] In this study, individuals in the highest quintile of Lp-PLA_2 levels demonstrated a doubling of the coronary event risk as compared with the lowest quintile.[9] Another prospective cohort study of 12,819 healthy middle-aged participants with lower LDL levels (median LDL < 130 mg/dL), Lp-PLA_2 mass independently predicted risk of incident coronary heart disease and subsequent coronary events. The latter were 3 times greater in individuals with mildly elevated Lp-PLA_2 levels than in patients with low Lp-PLA_2 and CRP levels.[15] Another investigation of 7983 subjects older than 55 years also found Lp-PLA_2 to be an independent predictor of CAD and ischemic stroke in the general population.[16]

In addition, 2 large studies have found Lp-PLA_2 to be prognostically useful in patients with documented CAD. The first study measured Lp-PLA_2 in 3766 patients with stable CAD and found it to be a significant predictor of nonfatal adverse cardiovascular outcomes independent of traditional clinical risk factors and CRP.[17] In the second study, Lp-PLA_2 levels were measured on 1051 coronary patients who were followed for 4 years. Elevated Lp-PLA_2 levels were associated with future cardiovascular events in this population, with a hazard ratio of 2.4 for the top tertile of Lp-PLA_2 activity as compared with the bottom tertile.[18]

Data from the Women's Health Study also confirm that women with the highest levels of Lp-PLA_2 at baseline (> 95th percentile) have an increased risk of future cardiovascular events. Upon multivariate analysis, the association between Lp-PLA_2 mass and CVD was markedly attenuated and insignificant after risk factor adjustment. Nevertheless, this study was limited by the short-term follow-up of 3 years, and it did not account for potential confounding variables, including hormone replacement therapy and antilipidemic medications, which lower Lp-PLA_2 and reduce CVD risk.[19]

Most lipid-modifying drugs reduce plasma Lp-PLA_2 mass as a general reflection of atherosclerotic disease activity.[20] Statins alone reduce Lp-PLA_2 by approximately 30%. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In

Myocardial Infarction (PROVE IT–TIMI 22) trial, plasma levels of Lp-PLA_2 were measured at baseline and 30 days after patients received medical therapy for an acute coronary syndrome.[21] Patients with 30-day Lp-PLA_2 activity in the highest quintile were at significantly increased risk of recurrent cardiovascular events compared with those in the lowest quintile (26.4% vs 17.6%; $P < .002$).[22] This study demonstrated that intensive statin therapy with atorvastatin 80 mg/d was associated with a 20% reduction in Lp-PLA_2 activity, independent of LDL, as well as a 23% decrease in Lp-PLA_2 mass.[21]

Darapladib is the first agent under clinical development in a new class of drugs called azetidinone inhibitors that inhibit Lp-PLA_2. In coronary patients, darapladib produced sustained inhibition (> 50%) of plasma Lp-PLA_2 activity when compared with placebo in a randomized clinical trial of 959 participants. Over the 12-week study period, the observed inhibition of Lp-PLA_2 activity was sustained at approximately 43%, 55%, and 66% for darapladib 40 mg, 80 mg, and 160 mg, respectively. Trials to establish if Lp-PLA_2 inhibition reduces mortality or stabilizes high-risk lesions are currently underway.[22,23]

Myeloperoxidase

Myeloperoxidase is a proatherogenic peroxidase enzyme produced by neutrophils that promotes vascular dysfunction and oxidation of lipoproteins in various animal and human studies. One large population study of apparently healthy individuals living in the United Kingdom found that increased serum levels of myeloperoxidase were associated with an increased risk of future CAD over 8 years of follow-up.[24] In multivariate analysis, participants in the highest quartile had an increased risk (1.36) as compared with the lowest quartile; however, the relative risk was diminished in the presence of other risk factors.

Role of Multidetector Computed Tomography Angiography

The presence of asymptomatic atherosclerosis was detected in our patient by a dual-source, CTA scanner (Figures 1 and 2). Newer CTA scanners allow expanded imaging in a shorter portion of the cardiac cycle, decrease motion artifacts, and provide diagnostic scans at faster heart rates.[25-27] As compared with invasive coronary angiography, which only delineates the coronary lumen, coronary CTA can identify extraluminal and intraluminal plaque and roughly quantify it.[28,29] A recent study examining 1000 consecutive asymptomatic individuals found that 22% of the population had occult CAD, of whom 5% had significant CAD involving at least 1 artery.[30] However, at a mean follow-up of 15 months, only 15 cardiac events occurred. Thus, the authors concluded that although CTA can provide an insight into the presence of CAD in asymptomatic individuals, the antecedent risk of radiation exposure precludes using this as a screening tool. Before CTA can be recommended for this purpose, long-term follow-up data are required, especially for hard endpoints such as myocardial infarction and cardiac death. Currently, CTA in asymptomatic individuals is considered to be an inappropriate indication.

In young adults, Lp-PLA_2 mass is independently associated with the presence of coronary atherosclerosis and the amount of coronary calcium on CTA.[31] Vulnerable plaques form the culprit lesions that may rupture in individuals with CAD. CTA can noninvasively detect coronary artery stenoses, but characterization of the composition of plaques and detection of vulnerable plaques, which may not be calcified, may be missed on CTA. On the other hand, the calcification of atheroma occurs early in plaque development as part of the inflammatory pathophysiologic cascade, is actively regulated like bone mineralization, and is likely to justify the use of calcium as a signal for the potential for vulnerable plaque. Accordingly, CTA may be subsequently used to define unstable or vulnerable plaques apart from "stable" calcified plaque. Factors such as vascular function, plaque composition, plaque geometry and remodeling, inflammation, and collateralization all confound the relationships among plaque size, luminal narrowing, and clinical events.

Unlike Lp-PLA_2, CRP is not closely associated with calcification on CTA as documented by several studies.[31-34] CRP was not associated with the existence of calcified coronary plaque, a finding that is in agreement with other investigations using coronary calcium scores as the outcome.[32-34]

Conclusion

Current cardiovascular screening relies heavily on conventional risk factors, family history, the presence of CAD equivalents, and evaluation of serum cholesterol and its subfractions. Despite this, the presence of traditional risk factors does not identify most CAD patients, in that 62% of individuals with new cardiovascular events have 1 or no risk factors and are not consistently targeted for therapy.[35] Primary approaches to the management of lipids remains treatment of LDL and non-HDL to goal (Table 2). However, recent consensus guidelines urge that once primary goals are attained, apoB levels should be checked and treatment adjusted accordingly.[5]

Evidence from randomized trials, including JUPITER, suggests that a reduction in mortality following treatment of milder dyslipidemias may expand the utilization of biomarkers for early detection of CAD.[9] Elevation of inflammatory markers, such as Lp-PLA_2, myeloperoxidase, and CRP, may herald the onset of symptomatic atherosclerotic coronary disease in otherwise apparently healthy individuals. Furthermore, CTA and other technologies have become extremely sensitive at detecting CAD decades before acute events occur. Mortality data supporting the use of inflammatory biomarkers and cardiovascular imaging for routine screening of atherosclerotic disease activity are lacking on a population level.

Coronary CTA may someday be able to define stable versus unstable or vulnerable plaques, thereby allowing tailored approaches to treatment and intervention. Finally, for patients who are reluctant to initiate lifestyle modifications or who start and remain on cardioprotective medications, identification of early atherosclerosis with tools such as coronary CTA and the ability to monitor treatment effectiveness with biomarkers may be helpful in enhancing compliance with these therapeutic interventions.[36] ■

References

1. Kung H-C, Hoyert DL, Xu JQ, Murphy SL. *Deaths: Final Data for 2005*. National Vital Statistics Reports; vol 56, no 10. Hyattsville, MD: National Center for Health Statistics; 2008.
2. World Health Organization. The global burden of disease: 2004 update. http://www.who.int/healthinfo/global_burden_disease/en/. Published 2008. Accessed February 12, 2009.
3. Rosamond W, Flegal K, Furie K, et al, for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics–2008 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008;117:e25-e146.
4. McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet*. 2008;372:224-233.
5. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2008;51:1512-1524.
6. Cromwell WC, Otvos JD, Keyes MJ, et al. LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study—implications for management. *J Clin Lipid*. 2007;1:583-592.
7. Ingelsson E, Schaefer EJ, Contois JH, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA*. 2007;298:776-785.
8. Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men: prospective results from the Quebec cardiovascular study. *Circulation*. 1997;95:69-75.
9. Packard CJ, O'Reilly DS, Caslake MJ, et al, for the West of Scotland Coronary Prevention Study Group. Lipoprotein associated phospholipase A_2 as an independent predictor of coronary heart disease. *N Engl J Med*. 2000;343:1148-1155.
10. Ridker PM, Danielson E, Fonseca FA, et al, for the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195-2207.
11. Zacho J, Tybjaerg-Hansen A, Jensen JS, et al. Genetically elevated C-reactive protein and ischemic vascular disease. *N Engl J Med*. 2008;359:1897-1908.
12. Blake GJ, Ridker PM. Novel clinical markers of vascular wall inflammation. *Circ Res*. 2001;89:763-771.
13. Yang EH, McConnell JP, Lennon RJ, et al. Lipoprotein-associated phospholipase A_2 is an independent marker for coronary endothelial dysfunction in humans. *Arterioscler Thromb Vasc Biol*. 2006;26:106-111.
14. Lavi S, McConnell JP, Rihal CS, et al. Local production of lipoprotein-associated phospholipase A_2 and lysophosphatidylcholine in the coronary circulation: association with early coronary atherosclerosis and endothelial dysfunction in humans. *Circulation*. 2007;115:2715-2721.
15. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A_2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in

Main Points

- Cardiovascular disease (CVD) accounts for more deaths worldwide than any other cause of mortality, including infectious disease and other poverty-related causes.
- Approximately 50% of all acute coronary syndromes occur in previously asymptomatic subjects, 90% of whom have modifiable risk factors; yet our current screening approaches fail to prevent the 1.2 million acute cardiovascular events that occur annually in the United States.
- Data from a major international study showed that 9 potentially modifiable risk factors accounted for more than 90% of the risk for CVD.
- Many large-scale epidemiologic studies of most populations have described a significant dose-response relationship between baseline low-density lipoprotein (LDL) levels and reduction of LDL using pharmacotherapy and the subsequent risk of CVD.
- Potential biomarkers for disease activity include C-reactive protein, lipoprotein-associated phospholipase A_2, and myeloperoxidase. They may become useful tools for risk stratification or measurement of therapeutic efficacy.
- Newer computed tomography angiography scanners allow expanded imaging in a shorter portion of the cardiac cycle, decrease motion artifacts, and provide diagnostic scans at faster heart rates.

Communities (ARIC) study. *Circulation*. 2004; 109:837-842.
16. Oei HH, van der Meer IM, Hofman A, et al. Lipoprotein-associated phospholipase A_2 activity is associated with risk of coronary heart disease and ischemic stroke: the Rotterdam Study. *Circulation*. 2005;111:570-575.
17. Sabatine MS, Morrow DA, O'Donoghue M, et al for the PEACE Investigators. Prognostic utility of lipoprotein-associated phospholipase A_2 for cardiovascular outcomes in patients with stable coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2007;27:2463-2469.
18. Koenig W, Khuseyinova N, Lowel H, et al. Lipoprotein-associated phospholipase A_2 adds to risk prediction of incident coronary events by C-reactive protein in apparently healthy middle-aged men from the general population: results from the 14-year follow-up of a large cohort from southern Germany. *Circulation*. 2004;110:1903-1908.
19. Blake GJ, Dada N, Fox JC, et al. A prospective evaluation of lipoprotein-associated phospholipase A_2 levels and the risk of future cardiovascular events in women. *J Am Coll Cardiol*. 2001;38:1302-1306.
20. Saougos VG, Tambaki AP, Kalogirou M, et al. Differential effect of hypolipidemic drugs on lipoprotein-associated phospholipase A_2. *Arterioscler Thromb Vasc Biol*. 2007;27: 2236-2243.
21. O'Donoghue M, Morrow DA, Sabatine MS, et al. Lipoprotein-associated phospholipase A_2 and its association with cardiovascular outcomes in patients with acute coronary syndromes in the PROVE IT-TIMI 22 (PRavastatin or atorVastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction) Trial. *Circulation*. 2006;113:1745-1752.
22. Mohler ER, Ballantyne CM, Davidson MH, et al, for the Darapladib Investigators. The effect of darapladib on plasma lipoprotein-associated phospholipase A_2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease risk equivalent: the results of a multicenter, randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol*. 2008;51:1632-1641.
23. Blackie JA, Bloomer JC, Brown MJ, et al. The identification of clinical candidate SB-480848: a potent inhibitor of lipoprotein-associated phospholipase A_2. *Bioorg Med Chem Lett*. 2003;13:1067-1070.
24. Meuwese MC, Stroes ES, Hazen SL, et al. Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals: the EPIC-Norfolk Prospective Population Study. *J Am Coll Cardiol*. 2007;50:159-165.
25. Scheffel H, Alkadhi H, Plass A, et al. Accuracy of dual-source CT coronary angiography: first experience in a high pre-test probability population without heart rate control. *Eur Radiol*. 2006;16:2739-2747.
26. Ropers U, Ropers D, Pflederer T, et al. Influence of heart rate on the diagnostic accuracy of dual-source computed tomography coronary angiography. *J Am Coll Cardiol*. 2007;50:2393-2398.
27. Matt D, Scheffel H, Leschka S, et al. Dual-source CT coronary angiography: image quality, mean heart rate, and heart rate variability. *AJR Am J Roentgenol*. 2007;189:567-573.
28. Leber AW, Knez A, Becker A, et al. Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of coronary atherosclerotic plaques: a comparative study with intracoronary ultrasound. *J Am Coll Cardiol*. 2004;43:1241-1247.
29. Kitagawa T, Yamamoto H, Ohhashi N, et al. Comprehensive evaluation of noncalcified coronary plaque characteristics detected using 64-slice computed tomography in patients with proven or suspected coronary artery disease. *Am Heart J*. 2007;154:1191-1198.
30. Choi EK, Choi SI, Rivera JJ, et al. Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. *J Am Coll Cardiol*. 2008;52:357-365.
31. Iribarren C, Gross MD, Darbinian JA, et al. Association of lipoprotein-associated phospholipase A_2 mass and activity with calcified coronary plaque in young adults: the Cardia study. *Arterioscler Thromb Vasc Biol*. 2005;25: 216-221.
32. Hunt ME, O'Malley PG, Vernalis MN, et al. C-reactive protein is not associated with the presence or extent of calcified subclinical atherosclerosis. *Am Heart J*. 2001;141:206-210.
33. Redberg RF, Rifai N, Gee L, Ridker PM. Lack of association of C-reactive protein and coronary calcium by electron beam computed tomography in postmenopausal women: implications for coronary artery disease screening. *J Am Coll Cardiol*. 2000;36:39-43.
34. Reilly MP, Wolfe ML, Localio AR, Rader DJ. C-reactive protein and coronary artery calcification: the Study of Inherited Risk of Coronary Atherosclerosis (SIRCA). *Arterioscler Thromb Vasc Biol*. 2003;23:1851-1856.
35. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA*. 2003;290:898-904.
36. McCullough PA, Lepor NE. Lipids, biomarkers, and noninvasive imaging of atherosclerotic disease activity in clinical trials. *Rev Cardiovasc Med*. 2008;9:142-149.