Atherosclerosis—Know Your Risk—Is it Time for a Paradigm Shift?

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Abstract

Atherosclerosis is a form of arteriosclerosis characterized by the deposition of atheromatous plaques containing cholesterol and lipids on the innermost layer of the walls of large and medium-sized arteries. People with atherosclerosis have a higher risk for cardiovascular disease (CVD) and stroke. Modification of traditional risk factors, such as smoking cessation, decreasing blood pressure, and lowering of cholesterol in high-risk individuals, has resulted in reducing CVD and stroke remarkably. However, the current standard of care using traditional modifiable risk factors alone is frequently inadequate to identify some individuals with atherosclerosis. Therefore, it is important to not rely solely on risk factor modification when assessing for CVD, but also to incorporate a disease platform. A new paradigm focusing on the disease itself (atherosclerosis) is necessary. This article will review the tools necessary to identify disease and will examine why it is critical to know the cause of the disease and to develop a treatment plan to eradicate it.

Atherosclerosis continues to be the number one cause of death in the US. Annually, 1,000,000 people will suffer a myocardial infarction (MI): one-third of those will occur in people who have already suffered an event.[1] Despite treatment of major modifiable risk factors proved to reduce CVD,[2,3] the high recurrence rate raises serious questions that the current standard of care using modifiable risk factors to reduce MI is inadequate and that it is critical to start looking beyond the status quo. Framingham and Reynolds Risk Scores fail to identify the majority of people who will have an event.[4] Most MIs are caused by non-obstructing plaques of less than 50 % of the arterial lumen.[5,6] Traditional cardiology focuses on stress testing and angiography to assess MI risk ('lumenology'—is the lumen open?) The pitfall is that many people will still have atherosclerosis and be at high risk for a MI despite having a normal stress test or angiogram. A new paradigm ('arteriology'—is disease present?) using noninvasive tools such as carotid intima media thickness (cIMT), carotid and aortic ultrasound, and coronary calcium score (CCS) is necessary. If disease (atherosclerosis) is discovered, a comprehensive evaluation and treatment plan must be implemented to reduce the high recurrence rate of MI.

Arteriology—Is Disease Present?

Direct examination of the endothelium is important to determine if disease (atherosclerosis) is present or not. Patient identification is categorized as primary, secondary, or tertiary (see *Figure 1*). Primary means no disease is present; secondary means that disease is present but the patient has not had an MI or stroke; tertiary means the patient has suffered an MI or stroke.

cIMT is an excellent tool to detect and monitor plaque.[1] cIMT thickness and presence or absence of plaque improves prediction of CVD risk.[7,8] cIMT is noninvasive, inexpensive, repeatable without adverse effects, adds prognostic power to conventional risk stratification tools, and can be used to monitor the disease (atherosclerotic) process. CCS is another excellent tool to document the presence of atherosclerosis and identify patients at increased risk for CVD and stroke.[9–11] The calcium scale is a linear scale with 4 calcium score categories that correlate directly with risk for events and likelihood of obstructive CVD: <11 none; 11–99 mild; 100–400 moderate; >400 severe. CCS adds prognostic power to conventional risk stratification tools, alters therapeutic goals and improves compliance.

Genetic Assessment

You cannot get more personal than your genetic makeup. Several genetic genotypes provide valuable information that helps in identifying subjects potentially at risk for disease (atherosclerosis) and deciding the most effective treatment option to eradicate it.

1. Apolipoprotein E (Apo E) is a class of apolipoprotein found in the chylomicron and intermediate-density lipoprotein that is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. The gene responsible for Apo E is polymorphic with three common alleles: Apo E2, Apo E3, and Apo E4. Each subject has two copies of the allele, resulting in six common genotypes. Although these allelic forms differ from each other by only one or two amino acids, these differences alter Apo E structure and function that have physiologic consequences (see *Table 1*). Fish oil supplementation decreases triglycerides and small dense low-

Figure 1: Disease Identification—Primary, Secondary, and Tertiary
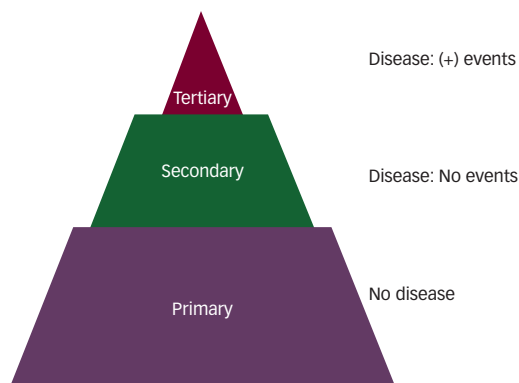
Table 1: Apolipoprotein E Genotypes

	Apo E2 Response		Apo E3 Response		Apo E4 Response	
Genotype	2/2	2/3	3/3	2/4	3/4	4/4
Population Frequency	1 %	10 %	62 %	2 %	20 %	5 %
Fish oil[12]	↓↓TG ↓small dense LDL ↑HDL		↓TG ↓small dense LDL ↑HDL		↓TG ↓↓small dense LDL ↓HDL ↑↑LDL	
Low fat diet[13,14]	↓LDL ↑small dense LDL		↓↓LDL ↔small dense LDL		↓↓↓LDL ↓small dense LDL	
Moderate fat diet[14]	↔LDL ↔small dense LDL		↓LDL ↓small dense LDL		↓LDL ↑↑small dense LDL	
Moderate alcohol[15]	↑HDL ↓LDL		↑HDL		↓HDL ↑LDL	

The table represents a summary of reported metabolic responses seen with different apolipoprotein (Apo) E genotypes. HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglyceride.

density lipoprotein cholesterol (LDL-C) in all three alleles; however, fish oil adversely decreases high-density lipoprotein cholesterol (HDL-C) and increases LDL-C in subjects with Apo E4.[12] A very low fat diet is extremely important for subjects with Apo E4 alleles because of its profound impact on decreasing LDL-C.[13,14] Modest alcohol consumption has a favorable impact on lipids with Apo E2 and E3 alleles but has an unfavorable impact on HDL-C and LDL-C in subjects with Apo E4 alleles.[15] It is important that subjects with Apo E4 alleles be educated on the potential negative impact that alcohol can have on their lipids and potential risk for atherosclerosis. Exercise significantly improves lipids in subjects with Apo E2 and E3 alleles, whereas that does not appear to be the case in subjects with Apo E4 alleles.[16] Furthermore, Apo E4 polymorphism increases the risk for exercise-induced silent myocardial ischemia.[17]

2. Kinesin-like protein 6 (*KIF6*) is a member of the molecular motor superfamily involved in the intracellular transport along microtubules. Statin studies suggest that carriers of a common polymorphism in the *KIF6* gene that leads to an arginine substitution for tryptophan at position 719 (Trp719Arg) might preferentially benefit from specific statin therapy, whereas *KIF6* noncarriers achieve little if any reduction in CVD. In the Cholesterol and Recurrent Events (CARE) study and West of Scotland Coronary Prevention Study (WOSCOPS) carriers of the *KIF6* 719Arg allele had an increased risk for coronary events, and pravastatin treatment substantially reduced that risk.[18] *KIF6* noncarriers however

did not receive significant benefit from pravastatin treatment despite a comparable reduction in LDL-C versus *KIF6* carriers. Similar results were observed in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT-TIMI 22) trial.[19] However, three other statin trials with rosuvastatin (Justification for the Use of Statins in Primary Prevention [JUPITER]) and simvastatin (Heart Protection Study [HPS] and Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering [IDEAL]) were equally effective in reducing CVD rates among carriers and noncarriers of the *KIF6* allele.[20–22] The *KIF6* 719Arg allele also increases vulnerability to LDL-C and thereby influences the expected clinical benefit of therapies that reduce LDL-C.[23] These findings suggest that *KIF6* carriers may have a higher lifetime risk for CVD and would benefit from any statin. A large meta-analysis of 19 case-control studies failed to show *KIF6* Trp719Arg polymorphism was associated with an increased risk for CVD.[24] The analysis, however, did not explore whether statin use modifies the effect of the 719Arg allele on risk as was performed in the WOSCOPS, CARE, and PROVE IT–TIMI 22 trials. Based on these findings it is prudent to prescribe simvastatin or rosuvastatin when statin treatment is considered in *KIF6* noncarriers at high risk for CVD, whereas any statin is effective in *KIF6* carriers. Although atorvastatin is widely prescribed in both men and women there is no clinical trial showing that atorvastatin decreases CVD in women.[25]

3. 9 region p21 locus (9p21). A number of highly correlated single nucleotide polymorphisms (SNPs) found in the chromosome 9p21 have been associated with MI, particularly early onset MI, and other manifestations of CVD. Associations with abdominal aortic aneurysm (AAA) and with intracranial aneurysm have also been reported.[26,27] Populations that have 9p21 polymorphism have an increased risk for MI, CVD, and AAA compared with 9p21 noncarriers. Individuals in the population that are homozygous for 9p21 have a 1.64 times greater risk for MI versus 9p21 noncarriers. The corresponding risk is 2.02 times as great for early-onset cases. The risk for AAA is 1.74 times greater in the homozygous 9p21 carrier compared with 9p21 noncarriers. In addition, homozygous carriers of 9p21 have a 1.47- and 1.60-fold increased risk for atherothrombotic and hemorrhagic strokes, respectively.[28] Make patients aware and perform annual aortic ultrasound.

4. Lipoprotein(a) (*LPA*) is a lipid-rich particle similar to LDL-C and has been determined to be an independent risk factor for CVD.[29] A variant in the *LPA* gene that substitutes a methionine residue for isoleucine at position 4399 (Ile4399Met) is associated with a significantly increased risk for CVD.[30] Subjects with the *LPA* genetic variant also have a higher risk for thrombosis and therefore may derive more benefit from the anti-thrombotic properties of aspirin therapy. Although aspirin therapy is a well-established treatment for patients with secondary and tertiary CVD, the benefit for primary prevention remains unclear. Current recommendations must consider the future risk for CVD weighed against the bleeding risk for aspirin. Any additional information that would aid in better defining the benefits of aspirin, and/or the risk for bleeding, has potential utility for clinicians who are making decisions on aspirin therapy in patients without disease (atherosclerosis). The Women's Health Study (WHS) examined the efficacy of aspirin therapy versus placebo for primary prevention of CVD in healthy women.[31] As anticipated, *LPA* levels in *LPA* carriers of the allele were elevated compared with *LPA* noncarriers and *LPA* carriers had a twofold increased risk for subsequent CVD versus noncarriers. In *LPA* carriers there

was a significant risk reduction associated with aspirin treatment (number needed to treat to prevent one major CVD event was 37. In contrast for *LPA* noncarriers, the number needed to treat to prevent one major CVD event was 625 and there were ~15 times more bleeds for each CVD event prevented. Among men and women nonusers of aspirin in the primary prevention Atherosclerosis Risk in Communities study, the carrier of the *LPA* variant was associated with increased risk for CVD.[32] This risk however was not found in aspirin users, findings consistent with results from the WHS. These results provide compelling evidence that carriers of the *LPA* variant derive significant benefit from aspirin therapy. Aspirin therapy should be recommended to both men and women who carry the *LPA* variant even in the absence of disease (atherosclerosis). Aspirin therapy however should be discouraged in the *LPA* noncarriers as the risk for bleeding outweighs the benefit of CVD reduction. Ethnic frequency of the *LPA* variant varies widely. While the frequency in the WHS, a predominately Caucasian population, was 3.7 %, the frequency is 16 % in the Chinese and Japanese population, and 28 % in the Hispanic population.

Inflammatory Biomarkers Assessment

Like with genetic genotypes, inflammatory biomarkers provide valuable information that helps in identifying subjects potentially at risk for disease (atherosclerosis) and deciding the most effective treatment options to eradicate it. *Table 2* outlines several inflammatory biomarkers for consideration as predictors of disease (atherosclerosis).

1. F2-Isoprostanes (F2-IsoPs). Oxidative reactions play a significant role in many biological conditions including chronic diseases, such as atherosclerosis. Oxidative modification of LDL-C and subsequent formation of foam cells are thought to be an initial step in atherogenesis.[33]

F2-IsoPs are formed *in vivo* from the reaction of oxygen-free radicals with arachidonic acid and have been found in oxidized LDL particles and atherosclerotic plaques. Traditional risk factors for atherosclerosis such as obesity, dyslipidemia, hypertension, diabetes, and smoking are associated with increased levels of F2-IsoPs in humans. Subjects with a greater number of risk factors had higher F2-IsoPs values. Each biomarker was associated with a higher odds ratio for CVD in univariate analysis, but only F2-IsoPs was associated with higher odds ratios for CVD using multivariate analysis.[34] This finding establishes F2-IsoPs values as a potential independent risk factor for CVD. Another study further established F2-IsoPs values as an independent risk factor for CVD.[35] When subjects were stratified by F2-IsoPs quartile, the odds ratio for subjects in the highest IsoP quartile to have angiographic evidence of CVD was 9.7 compared with subjects in the lowest F2-IsoPs quartile.[35] Adding F2-IsoPs values to the Framingham risk score significantly improved the ability to predict angiographic CVD compared with using the Framingham risk score alone, again demonstrating the potential clinical utility of measuring F2-IsoPs. However, additional clinical trials are required to fully investigate the potential benefits of measuring F2-IsoPs values in everyday clinical practice.

2. C-reactive protein (CRP) is an acute-phase protein produced by the liver in response to cytokine production during tissue injury, inflammation, or infection. Standard CRP tests determine levels that are increased up to 1,000-fold in response to infection or tissue destruction, but cannot adequately assess the normal range. High-sensitivity CRP (hs-CRP) assays detect levels of CRP within the normal range, levels proved to predict future CVD events.

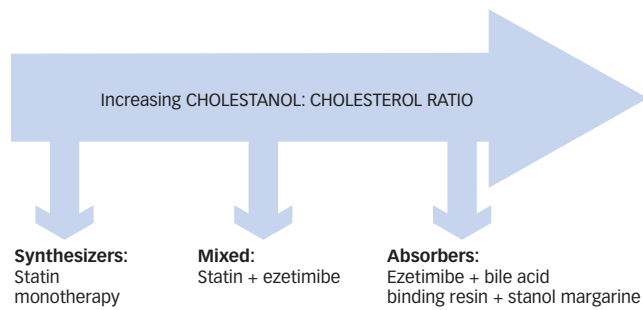## Table 2: Inflammatory Biomarkers for Consideration as Predictors of Atherosclerosis

- F2-Isoprostanes (F2-IsoPs)
- High-sensitivity C-reactive protein (hs-CRP)
- Urine albumin creatinine ratio (UACR)
- Myeloperoxidase (MPO)
- Lipoprotein-associated phospholipase A2 (Lp-PLA2)
- Fibrinogen
- Oxidized low-density lipoprotein (oxLDL)
- Homocysteine (Hcy)

High hs-CRP levels are associated with increased risks for mortality and major diseases including diabetes mellitus, hypertension, and CVD.[36] Data from the Physicians' Health Study demonstrated increasing levels of hs-CRP at study entry were associated with a dramatic increase in risk for future MI.[37] In the WHS there was a strong linear increase in hs-CRP levels based on the number of components of the metabolic syndrome from none to all five components.[38] This raises an important question? Is hs-CRP a player in the disease (atherosclerosis) process or simple a reflection of the underlying metabolic disorders? A large meta-analysis including 80,000+ subjects from the genomic-wide association study looked at 18 CRP SNPs. Despite the fact that some SNPs were associated with higher hs-CRP levels this was not associated with an increased risk for CVD.[39] These results provide compelling evidence that hs-CRP alone is not a player in the atherosclerotic process but rather a reflection of the underlying metabolic disorder.

3. Urine albumin creatinine ratio (UACR). So what is albuminuria? An elevated urinary albumin excretion is a marker of endothelial dysfunction that symbolizes the kidney's way to translate the existence of vascular damage. Albuminuria is an independent risk factor for CVD in men and women with diabetes or hypertension, the general population, and those with established CVD.[40] A UACR <30 mg albumin/gram creatinine (mg/g) is defined as normal albuminuria, between 30 and 300 mg/g as microalbuminuria, and >300 mg/g as macroalbuminuria.[41] Three landmark studies, Losartan Intervention For Endpoint, Heart Outcomes Prevention Evaluation, and Nord-Trøndelag Health Study showed that increased albumin excretion, even at near 'normal' levels were associated with increased CVD mortality and stroke.[42–44] The Framingham Heart Study showed a threefold risk for developing CVD when the UACR was >3.9 mg/g in men and >7.5 mg/g in women.[45] These findings along with those of the three landmark studies challenge the notion that UACR <30 g/mg indicates normal albumin excretion. Critical health professionals understand that albuminuria is an important independent risk factor for CVD and at levels well below current guidelines.

4. Myeloperoxidase (MPO) is a member of the heme peroxidase family and is abundantly expressed in neutrophil granulocytes. MPO produces hypochlorous acid (HOCl) from hydrogen peroxide and chloride anion. Furthermore, MPO oxidizes tyrosine to tyrosyl radical using hydrogen peroxide as an oxidizing agent. Hypochlorous acid and tyrosyl radical are cytotoxic, so they are used by the neutrophil to kill bacteria and other pathogens, an important innate infectious disease host defense. Despite its major role in host defense, MPO has also been involved in pathologic states. During chronic inflammation or acute oxidative stress, MPO is released into the extracellular space where oxidants can be produced and host tissues damaged. Apolipoprotein B-100 is the unique protein of

Figure 2: Categorization of Dyslipidemia and Suggested Line(s) of Therapy

Increasing CHOLESTANOL: CHOLESTEROL RATIO

Synthesizers:
Statin
monotherapy

Mixed:
Statin + ezetimibe

Absorbers:
Ezetimibe + bile acid
binding resin + stanol margarine

LDL-C and is the major target of MPO. MPO rapidly adsorbs at the surface of LDL-C, promoting oxidation of amino acid residues and formation of oxidized lipoproteins triggering inflammation and atherosclerosis plaque formation.[46] HOCl selectively targets tyrosine residues to generate a stable product: 3-chlorotyrosine. Chlorination of the phenolic ring of tyrosine may have clinical relevance because elevated 3-chlorotyrosine products have been detected in LDL-C isolated from human atherosclerotic lesions.[47] Furthermore, HOCl selectively targets tyrosine residues in Apo A1, which accounts for 70 % of the total protein content of HDL. Increased 3-chlorotyrosine levels in HDL impair the ability of HDL apolipoproteins to remove cholesterol from macrophages in the artery wall essentially converting HDL from an anti-inflammatory to a pro-inflammatory state.[48] The limitation of the serum HDL-C level is that it does not assess HDL's functional properties. Even within a normal individual, HDL may become transiently pro-oxidant in the presence of systemic inflammation. Determination of HDL anti-inflammatory/proinflammatory function will likely provide important additional information beyond that available from simply knowing the quantitative level of HDL-C.[49]

5. Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyzes phospholipids. Lp-PLA2 is predominantly bound to LDL-C and ApoB containing lipoprotein, is highly expressed in the necrotic core of atherosclerotic plaques and has been associated with atherosclerotic plaque instability. Degradation of oxidatively modified phospholipids by this enzyme leads to the formation of pro-inflammatory and cytotoxic mediators.[50] Clinical studies have shown an association between elevated Lp-PLA2 levels and risk for both MI and stroke.[51] Therapies directed at lowering Lp-PLA2 levels may represent a novel approach to reducing vascular risk, though direct clinical benefit from targeting treatment to Lp-PLA2 levels remains unproved. Statin therapy is the most clearly established intervention to effectively lower Lp-PLA2 levels. Diminished levels of Lp-PLA2 associated with statin treatment can be at least partially attributable to parallel reductions in levels of LDL-C and ApoB.[52] The strength of the independent association of Lp-PLA2 with vascular disease is reduced after adjustment for baseline lipids and apolipoproteins.[53] Darapladib, a selective inhibitor of the Lp-PLA2 enzyme, was evaluated in two large-scale phase III clinical trials: Stabilization of Atherosclerotic Plaque By Initiation of Darapladib Therapy (STABILITY) and Stabilization of Plaque Using Darapladib-Thrombolysis in Myocardial Infarction (SOLID-TIMI 52).[54,55] The results of the two studies were recently published. The STABILITY trial failed to meet the primary endpoint: time to first occurrence of any major

adverse cardiovascular event.[56] In the SOLID-TIMI 52 trial, direct inhibition of Lp-PLA2 with darapladib added to optimal medical therapy in patients who experience an acute coronary event did not reduce the of risk for major coronary events.[57] The results raise questions about the therapeutic utility of Lp-PLA2 inhibition in the treatment of atherosclerosis.

6. Fibrinogen may be associated with the risk for CVD and stroke. In a large individual participant meta-analysis, moderately strong associations were found between usual plasma fibrinogen level and the risks for CHD, stroke, and other vascular and nonvascular mortality.[58]

7. Oxidized LDL (oxLDL) is thought to play a major role in inflammatory response in the arterial vessel wall. Elevated concentrations of oxLDL are predictive of future CVD in apparently healthy men.[59] Higher concentrations of oxidized LDL are associated with increased incidences of the metabolic syndrome.[60] Thus, oxLDL represents a promising risk marker for clinical CVD complications and should be evaluated in further studies.

8. Homocysteine (Hcy). The mechanism by which Hcy exerts atherosclerosis effects is now being elucidated. The working hypothesis is that elevated Hcy level promotes oxidant injury to the vascular endothelium, impairs endothelium-dependent relaxation, and alters the coagulant properties of blood. Hcy level (>15 umol/l) significantly predicted CVD in the Multi-Ethnic Study of Atherosclerosis (MESA) trial and CVD in the National Health and Nutrition Examination Survey (NHANES) III, after adjustments for traditional risk factors.[61] Any individual with an Hcy >15 umol/l should be evaluated for atherosclerosis. Whether lowering Hcy reduces vascular events remains unclear.

Other Root Causes

1. Insulin resistance (IR) is a typical feature of type 2 diabetes mellitus but is observed in several other common clinical conditions and also in many apparently healthy subjects. IR is strongly related to several classic CVD risk factors, such as obesity, high triglycerides, low HDL, hypertension, and albuminuria.[62] Also IR is related to many nontraditional risk factors such as CRP, plasminogen activator inhibitor-1, fibrinogen, and other markers of inflammation.[61] Therefore, it is not surprising that IR is present in the majority of MI and stroke patients.[63,64] While there are several ways to identify those patients that are at increased risk for IR (the metabolic syndrome risk factors and triglycerides/HDL-C ratio) the 'gold' standard is the 2-hour oral glucose tolerance test. If the fasting glucose is >100 mg/dl, 1-hour value >125 mg/dl, or the 2-hour value >120 mg/dl the patient has IR and is at increased risk for CVD and stroke.[65]

2. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) are two proteins that are cleaved from pro-BNP. Both NT-proBNP and BNP levels are used for screening, diagnosis of heart failure, and may be useful to establish prognosis in heart failure, as both markers are typically higher in patients with worse outcome.[66] Subjects with a NT-proBNP level <125 pg/ml are at low risk for heart failure (i.e. 'happy heart'), whereas values >125 pg/ml are associated with an increased risk for asymptomatic left ventricular dysfunction and at risk for heart failure. The Role of N-Terminal Pro-Brain Natriuretic Peptide and Echocardiography for Screening Asymptomatic Left Ventricular Dysfunction in a Population at High Risk for Heart Failure (PROBE-HF) study assessed NT-proBNP and echocardiography in 1,012 subjects with hypertension and/or diabetes and

no symptoms or signs of heart failure.[67] Fifty-two (5.1 %) of the subjects had NT-proBNP values >125 pg/ml and demonstrated systolic and moderate-to severe diastolic dysfunction on echocardiography. The importance of heart failure was highlighted at the 2013 European Association for the Study of Diabetes 49th Annual Meeting. A joint session with the European Society of Cardiology was dedicated to this topic, 'Heart failure and diabetes: a deadly intersection.'[68] The presenters discussed heart failure risk in patients with diabetes, as well as the importance of further investigation into the safety of commonly used diabetes treatments in patients with heart failure. Only seven of 12 major CVD outcome trials actually reported heart failure as an outcome and, worse still, of the 24 major diabetes-outcome trials, only 10 reported heart-failure outcomes. More alarming is that of 16 CVD outcomes trials for diabetes drugs either in development or already under way, NOT a single one of them will report heart failure as part of the primary outcome. All subjects with hypertension and diabetes should be tested for NT-proBNP. Any subject with a NT-proBNP >125 pg/ml is at risk for heart failure and should be treated aggressively. In subjects with diabetes it is prudent to select drug classes that are not know to impact adversely on heart failure.

3. Obstructive sleep apnea (OSA) is characterized by recurrent episodes of complete or partial collapse of the upper airway during sleep, resulting in apneas or hypopneas, respectively. OSA is independently associated with death from CVD, including MI and stroke known complications of atherosclerosis. Identify subjects at increased risk for OSA is important because treatment of OSA with continuous positive airway pressure may attenuate atherosclerosis.[69]

4. Vitamin D. Deficiency of vitamin D is now recognized to be highly prevalent worldwide. Considerable evidence indicates vitamin D deficiency is extremely prevalent and associated with increased CVD and all-cause mortality. Although assessment of 25(OH)D levels is reasonable for many adults, especially those with CVD or high CVD risk, and treatment can easily be accomplished, definitive randomized controlled trials are needed to determine whether vitamin D therapy will live up to its hype.[70]

5. Smoking is a major health hazard contributing significantly to CVD morbidity and mortality. Smoking influences all phases of atherosclerosis from endothelial dysfunction to acute clinical events, the latter being largely thrombotic.[71] Smoking cessation must continue to be a national priority.

6. Periodontal disease (PD). A link between oral health and CVD has been proposed for more than a century. Recently, possible links between PD and CVD has intensified since these two disorders share several common risk factors, including age, cigarette smoking, and diabetes mellitus. Observational studies support an association between PD and CVD independent of known confounders. They do not, however, support a causative relationship. Although periodontal interventions result in a reduction in systemic inflammation and endothelial dysfunction in short-term studies, there is no evidence that they prevent CVD or modify its outcomes.[72]

7. Plant sterols. Total body cholesterol pools represent a balance between endogenous synthesis and dietary absorption. Plasma sterols lathosterol and desmosterol serve as markers of cholesterol synthesis, while campesterol, sitosterol, and cholestanol are markers of fractional cholesterol absorption. The benefit of statins has largely been linked to total cholesterol and LDL-C lowering, and it has been suggested that the degree of lowering may relate to reductions in synthesis markers, which may be offset by increases in markers of absorption. Statins markedly lower cholesterol synthesis, but also significantly increase fractional intestinal cholesterol absorption.[73,74] In a subset of CVD patients participating in the Scandinavian Simvastatin Survival Study (4S) those in the highest quartile of the cholestanol/C ratio (indicative of high cholesterol absorption), while on simvastatin had no reduction in CVD events compared with the placebo-treated group, with the converse also being the case.[75] Since statin therapy is often long term, measuring sterols may prove to be a useful tool for optimizing dyslipidemia therapy and reducing CHD risk (see *Figure 2*).

Conclusion

Atherosclerosis continues to be the number one cause of death in the US. Aggressively treating major modifiable risk factors significantly reduces the risk for CVD and stroke. However, the current standard of care using risk factor identification and modification alone fails to identify some people at risk. Noninvasive endothelial testing, genetics assessment, and measurement of major biomarkers enhance the ability to identify disease (atherosclerosis) earlier. When disease is found, the causes must be identified and treated. A paradigm shift focusing on arteriology is mandated to reduce the high rate of recurrence of MI and stroke. ■

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