

Molecular sources of residual cardiovascular risk, clinical signals, and innovative solutions: relationship with subclinical disease, undertreatment, and poor adherence: implications of new evidence upon optimizing cardiovascular patient outcomes

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Abstract: Residual risk, the ongoing appreciable risk of major cardiovascular events (MCVE) in statin-treated patients who have achieved evidence-based lipid goals, remains a concern among cardiologists. Factors that contribute to this continuing risk are atherogenic non-low-density lipoprotein (LDL) particles and atherogenic processes unrelated to LDL cholesterol, including other risk factors, the inherent properties of statin drugs, and patient characteristics, ie, genetics and behaviors. In addition, providers, health care systems, the community, public policies, and the environment play a role. Major statin studies suggest an average 28% reduction in LDL cholesterol and a 31% reduction in relative risk, leaving a residual risk of about 69%. Incomplete reductions in risk, and failure to improve conditions that create risk, may result in ongoing progression of atherosclerosis, with new and recurring lesions in original and distant culprit sites, remodeling, arrhythmias, rehospitalizations, invasive procedures, and terminal disability. As a result, identification of additional agents to reduce residual risk, particularly administered together with statin drugs, has been an ongoing quest. The current model of atherosclerosis involves many steps during which disease may progress independently of guideline-defined elevations in LDL cholesterol. Differences in genetic responsiveness to statin therapy, differences in ability of the endothelium to regenerate and repair, and differences in susceptibility to nonlipid risk factors, such as tobacco smoking, hypertension, and molecular changes associated with obesity and diabetes, may all create residual risk. A large number of inflammatory and metabolic processes may also provide eventual therapeutic targets to lower residual risk. Classically, epidemiologic and other evidence suggested that raising high-density lipoprotein (HDL) cholesterol would be cardioprotective. When LDL cholesterol is aggressively lowered to targets, low HDL cholesterol levels are still inversely related to MCVE. The efflux capacity, or ability to relocate cholesterol out of macrophages, is believed to be a major antiatherogenic mechanism responsible for reduction in MCVE mediated in part by healthy HDL. HDL cholesterol is a complex molecule with antioxidative, anti-inflammatory, anti-thrombotic, antiplatelet, and vasodilatory properties, among which is protection of LDL from oxidation. HDL-associated paraoxonase-1 has a major effect on endothelial function. Further, HDL promotes endothelial repair and progenitor cell health, and supports production of nitric oxide. HDL from patients with cardiovascular disease, diabetes, and autoimmune disease may fail to protect or even become proinflammatory or pro-oxidant. Mendelian randomization and

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other clinical studies in which raising HDL cholesterol has not been beneficial suggest that high plasma levels do not necessarily reduce cardiovascular risk. These data, coupled with extensive preclinical information about the functional heterogeneity of HDL, challenge the “HDL hypothesis”, ie, raising HDL cholesterol per se will reduce MCVE. After the equivocal AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) study and withdrawal of two major cholesteryl ester transfer protein compounds, one for off-target adverse effects and the other for lack of efficacy, development continues for two other agents, ie, anacetrapib and evacetrapib, both of which lower LDL cholesterol substantially. The negative but controversial HPS2-THRIVE (the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) trial casts further doubt on the HDL cholesterol hypothesis. The growing impression that HDL functionality, rather than abundance, is clinically important is supported by experimental evidence highlighting the conditional pleiotropic actions of HDL. Non-HDL cholesterol reflects the cholesterol in all atherogenic particles containing apolipoprotein B, and has outperformed LDL cholesterol as a lipid marker of cardiovascular risk and future mortality. In addition to including a measure of residual risk, the advantages of using non-HDL cholesterol as a primary lipid target are now compelling. Reinterpretation of data from the Treating to New Targets study suggests that better control of smoking, body weight, hypertension, and diabetes will help lower residual risk. Although much improved, control of risk factors other than LDL cholesterol currently remains inadequate due to shortfalls in compliance with guidelines and poor patient adherence. More efficient and greater use of proven simple therapies, such as aspirin, beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, combined with statin therapy, may be more fruitful in improving outcomes than using other complex therapies. Comprehensive, intensive, multimechanistic, global, and national programs using primordial, primary, and secondary prevention to lower the total level of cardiovascular risk are necessary.

Keywords: cardiovascular prevention, low-density lipoprotein, high-density lipoprotein, statin drugs, metabolic syndrome, obesity, diabetes, niacin, AIM-HIGH study, cholesteryl ester transfer protein, endothelial progenitor cells, fibrate drugs

Introduction

Statins are the most frequently prescribed agents for primary and secondary prevention of coronary heart disease, the leading cause of death globally. While these agents have revolutionized the practice of cardiology, no new classes of antiatherosclerotic pharmaceuticals with major clinically proven benefits have appeared since the introduction of statins in 1987. Despite striking reductions in low-density lipoprotein (LDL) cholesterol levels, their ability to affect plaque reduction¹ and regression, associated with remarkable improvement in major cardiovascular events (MCVE), unwanted events continue in statin-treated patients who achieve LDL cholesterol goals, an ongoing exposure termed “residual risk.” Even after an unprecedented fall in cardiac mortality in developed countries, partly attributable to greater use of statins, coronary heart disease and stroke still account for >25% of all deaths.

Moreover, despite statin prescriptions at record levels, the current epidemic of cardiovascular risk remains one of the most important in human history.^{2–4} Unacceptably high levels of subclinical and undetected or silent disease are persisting challenges, reflected in part by the approximately 45% of sudden cardiac deaths in persons succumbing to coronary heart disease with no prior evidence of clinical heart disease.⁵

Much has been written about epidemiologic and other supporting data that strongly suggest high-density lipoprotein (HDL) cholesterol levels independently predict

cardiovascular disease.^{6,7} Raising HDL cholesterol has been a major goal in the quest to reduce residual risk. Recent evidence and experience, however, reflect the intricate composition and properties of HDL, and chronicle the difficulty in establishing quantity as a suitable surrogate for the protective actions of HDL cholesterol. Many factors, ranging from triglyceride and triglyceride-rich lipoprotein moiety concentrations, pathophysiology unrelated to the concentration of LDL cholesterol, and therapeutic control of coexisting risk factors, even encompassing patient, physician, and societal behaviors affecting outcome may all contribute to residual risk, and are explored in this review.

Residual risk remaining after treatment is greater than the risk that is eliminated

After LDL cholesterol targets are achieved, correcting any remaining lipid abnormalities with agents to raise total HDL cholesterol and lower triglyceride levels, if they were available, might indeed reduce cardiovascular risk and improve outcomes. However, the problem of residual risk and imperfections in risk reduction is substantially greater and more complex than was formerly appreciated. Evidence-based pharmacologic remedies to treat low HDL cholesterol levels, perhaps <40 mg/dL in men and <50 mg/dL in women (average levels, 45 mg/dL [1.15 mmol/L] in men; 55 mg/dL [1.4 mmol/L] in women), and triglycerides of 150–500 mg/

dL (1.71–5.7 mmol/L), still regarded as holy grails, are distant. The origin of residual risk is multifactorial, and new sources and pathways via which risk may be generated continue to be uncovered. As incomplete evidence supporting former views and therapies is re-examined, several central questions remain unanswered. The most important of these are how much residual risk can be eliminated pharmacologically and what is the most efficient and safe way to do so in which patients? If one also considers the impact of unfavorable global epidemics of obesity, metabolic syndrome, and type 2 diabetes, it becomes apparent that expanded solutions with greater scope and dimension will be essential for any meaningful success against this foe. To put this problem into perspective, the latest National Health and Nutrition Examination Survey (NHANES) data suggest that 53% of US adults have lipid abnormalities, of whom 27% have high LDL cholesterol, 23% have low HDL cholesterol, and 30% have high triglyceride levels.⁸ The sources of cardiovascular risk have changed over the last two decades, with a fall in LDL cholesterol, usually attributed to decreased tobacco use, increasing use of statins, less consumption of trans fatty acids, and as yet unexplained factors.^{9,10} Simultaneously, the phenotype of the typical patient with acute coronary syndrome of yesteryear was a thin, anxious, chain-smoking executive with high levels of LDL cholesterol, compared with the contemporary overweight, sedentary patient with a greater risk due to diabetes, metabolic syndrome, and high triglyceride/low HDL cholesterol levels.

A number of randomized controlled trials over the years indicate that in secondary prevention, ie, 4S (the Scandinavian Simvastatin Survival Study), LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease), CARE (Cholesterol And Recurrent Events), HPS (Heart Protection Study), TNT (Treat to New Targets), and PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) as well as in primary prevention, ie, WOSCOPS (West of Scotland Coronary Prevention Study), AFCAPS (Air Force/Coronary Atherosclerosis Prevention Study), and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), the plot of the cardiovascular event rate versus plasma LDL cholesterol attained is linear, and extrapolation of the regression line to zero events occurs at an LDL cholesterol level of about 40 mg/dL. However, in these studies of primary prevention patients, and in JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), residual events continue, even when well accepted target goals are attained.^{11–22} The risk reduction ranges from approximately 25% in LIPID, CARE, and HPS

up to an uncommonly high 45%.²² In diabetic patients, among whom atherosclerosis is responsible for about 80% of deaths, HPS reported a 22% risk reduction and 78% residual risk after treatment with simvastatin, and CARDS (the Collaborative Atorvastatin Diabetes Study) reported a 32% risk reduction and a 68% residual risk after atorvastatin therapy.¹⁰ In the major classical trials (4S, LIPID, CARE, HPS, AFCAPS/TexCAPS, WOSCOPS), reduction in LDL cholesterol averaged 28.5% and the percentage of MCVE not prevented by statins averaged 69.3%. As a rule of thumb, for patients taking statins in the large outcomes studies, about two thirds of MCVE continues. Further, patients in clinical trials receive different care from those in the community, and LDL cholesterol targets may not be reached as often in the real world. This is true in primary and secondary prevention,^{23–25} whether patients do or do not have diabetes.^{26–28} Although “lower is better” as far as patients with high risk or acute coronary syndrome are concerned,²⁹ even after aggressive statin therapy (LDL cholesterol <70 mg/dL) residual risk remains high.³⁰ In the TNT trial, those who received atorvastatin 80 mg enjoyed a 22% relative risk reduction in MCVE versus those who were treated with atorvastatin 10 mg, but 9% of patients still suffered an MCVE within 5 years.³¹ Similarly, in the CTT (Cholesterol Treatment Trialists) Collaborators meta-analyses, every 1 mmol/L fall in LDL cholesterol was accompanied by a 21% reduction in MCVE, but 5-year event rates in statin-treated patients were 14% compared with 18% in the nontreated group, and an even higher residual risk was evident in those with pre-existing coronary heart disease or type 2 diabetes.^{32,33} Over half of individuals who present with acute coronary syndrome do not have elevated LDL cholesterol levels, given that in today’s patients, who have a greater probability of being overweight with comorbidities and atherogenic dyslipidemia, factors other than LDL cholesterol are more likely to account for a sizeable portion of cardiovascular risk.

A revealing illustration of ongoing risk despite ideal medical therapy leading to disease progression was provided recently by Zellweger et al³⁴ from BASKET (the Basel Stent Kosten-Effektivitäts Trial), in which patients were followed for 5 years after successful complete revascularization. In addition to recurrence at culprit lesion sites, almost 40% of patients showed new perfusion defects in areas remote from the sites at which stents were originally placed. Most defects were silent, so that if single photon emission computed tomography had not been scheduled as part of the study, progression would have remained undetected. As a result, based on clinical events alone, coronary heart disease progression

would be significantly underrecognized. Parenthetically, there was no difference in progression whether the stents were bare or drug-eluting. BASKET extends results from other studies that identify plaque progression in lesions that are initially nonculprit, in remote locations, and at original culprit sites not due to stent failure.^{34,35}

The REACH (Reduction of Atherothrombosis for Continued Health) registry also called attention to the high event rate among stable patients with either high cardiovascular risk or coronary heart disease, and the appreciable association with multivessel disease, prior myocardial infarction, and diabetes.^{36,37} Overall, MACE rates were 14.4% for patients with established atherosclerotic disease in the first year of follow-up. When hospitalization was included in the composite endpoint, event rates reached 26.3% in patients with disease in three arterial beds within 4 years.³⁷

Further evidence for progression of coronary heart disease despite aggressive lowering of LDL cholesterol comes from intravascular ultrasound studies. Bayturan et al³⁸ found that over 20% of patients titrated to a mean LDL cholesterol of 58 mg/dL (1.5 mmol/L) continued to have an increase in plaque volume, which was associated with low HDL cholesterol, diabetes, and elevations in systolic blood pressure. All these data are consistent with the view, supported by pathologic and tracking studies, that coronary heart disease is a lifelong disease that begins in childhood and develops over decades, sometimes with spurts and stalls, is slowed by statin therapy, but still progresses because sufficient substrate remains unchanged. The presence of undetected risk factors and subclinical atherosclerosis in otherwise healthy people also creates a detection gap that leaves a large proportion of patients with coronary heart disease in whom the initial manifestation of the disease may be their last.

Six years ago, Dr Peter Libby, a pioneer and authority in inflammation and vascular biology, called attention to the “forgotten majority” of patients who continue to suffer events despite statin therapy.³⁹ The possibilities proposed included intervention that was too little, too late, and for too short a period of time. However, comparative physiologic data regarding low species-specific LDL cholesterol values, low human neonatal levels of LDL cholesterol,⁴⁰ epidemiologic associations of reduced rates of coronary heart disease in countries with lower LDL cholesterol values,⁴¹ and data from the aforementioned statin studies all support a central role of LDL in atherosclerosis. Moreover, in patients with *proprotein convertase subtilisin/kexin type 9* (*PCSK9*) gene polymorphisms leading to hypofunction, catalytic degradation of the LDL receptor is

impaired, and resulting low levels of LDL cholesterol are associated with a markedly lower incidence of coronary heart disease.^{42,43} However, as important as it is, there is more than LDL cholesterol at work during atherogenesis reflected in residual risk; hence, there must be more to an effective therapeutic response.

What steps in the pathogenesis of atherosclerosis involve more than LDL?

Atherosclerosis is a process in which disordered lipid metabolism results in an immunoinflammatory reaction that may be regarded as an aberrant defense. The currently accepted pathogenesis of atherosclerosis is multimechanistic, with reactions occurring continuously rather than in discrete steps, each one molecularly complex, involving intersecting pathways, and rich cross-talk horizontally and vertically.^{44–46} The model is LDL-centric, revolving around subintimal binding to proteoglycans in the extracellular matrix, LDL aggregation, and oxidative modification of LDL cholesterol, leading to retention in the arterial wall, but includes other factors, some of which may create residual risk. For instance, LDL cholesterol may be modified via nonoxidative mechanisms, lipoproteins may contribute to atherogenesis independently of LDL oxidation,⁴⁷ reactive oxygen species serve as intracellular messengers and may exert atherogenic effects independently of LDL “prior to” LDL oxidation, and cholesterol crystals may activate inflammasomes to induce atherogenic inflammatory reactions.⁴⁸ Glycation and modification of LDL cholesterol by methylglyoxal, a reactive dicarbonyl metabolite,⁴⁹ are both proatherogenic, albeit through different mechanisms. Among the several modifications of LDL cholesterol that occur, oxidation and aggregation are quantitatively the most important. Modification of LDL initiates not only direct proatherogenic processes but also the consequences of altered immunogenicity of the resulting epitopes, involving both innate and adaptive responses.⁵⁰

This model includes an ever-growing role for inflammatory pathways, which present a number of potential therapeutic targets that influence residual risk. Dysfunctional endothelium, in connection with loss of bioavailability of nitric oxide, releases adhesion molecules even before retention of LDL cholesterol can be identified in the arterial wall, promoting recruitment, binding, and migration of lymphocytes and monocytes to the lesion. Simultaneously, the subendothelial space is bathed with reactive oxygen species capable of oxidizing LDL. Activated endothelium also initiates prothrombotic changes that begin a long link between

inflammation and thrombosis that weaves throughout the natural history of coronary heart disease.^{51–53} Clearly, the endothelium participates in many early inflammatory steps, as it loses another of its homeostatic functions, ie, maintaining a nonadherent luminal surface. Inflammation alone, without accumulation or retention of LDL cholesterol, may produce arterial changes,^{54,55} and inflammation also controls development, progression, and destabilization of plaque. Much of the cross-talk mentioned, in large part mediated by cytokines and chemokines, occurs between monocytes/macrophages and vascular cells. Chemoattractant molecules produced by endothelial and smooth muscle cells recruit monocytes, primarily the proinflammatory subtype initially, which adhere through endothelial cell ligands, enter the subendothelial space, differentiate into macrophages, and accumulate lipid via scavenger receptors to become foam cells.⁵⁶ Phagocytic caveolae, which are sites strongly associated with cholesterol homeostasis and signal transduction, contain the structural protein, caveolin-1. Increased activity of caveolin-1, mediated by activation of transcription factor early growth response 1, promotes monocyte to macrophage differentiation, a possible critical step in atherogenesis.⁵⁷ Suppression of monocyte/macrophage caveolin-1 would be expected to inhibit foam cell formation and impede atherogenesis.

In lesional macrophages, enlargement of lipid droplets occurs when cholesterol delivery and storage is greater than cholesterol removal. A current topic in atherogenesis is macrophage cholesterol efflux, ie, the removal of cholesterol from cells, and a crucial step in the reverse cholesterol transport that modulates the development of foam cells. There are four main efflux pathways involved:

- aqueous diffusion of cholesterol away from peripheral cells, passively follows the concentration gradient
- scavenger receptor class B type 1, found in membranes of many tissues, particularly the liver, facilitates transfer of cholesterol from cell membranes to HDL peripherally, and from HDL to hepatocytes centrally, completing the reverse cholesterol transport limb
- ATP-binding cassette transporter A-1, present in macrophages, the liver, and the intestine, actively transports cholesterol to lipid-poor apolipoprotein A-I (ApoA-I) particles
- ATP-binding cassette transporter G-1, transports cholesterol to larger HDL moieties.

As atheromata evolve, accumulation of foam cells and apoptosis contribute to formation of a necrotic core within plaques, and it is within this core that most immune cell death occurs. In response to oxidized LDL cholesterol, as well as

other oxidized phospholipids and growth factors, including associated changes in genetic expression and transcriptional regulators, medial smooth muscle cells dedifferentiate, proliferate, and migrate to the intima. Such dedifferentiation from a quiescent, nonproliferative, and contractile phenotype to a proliferative, migratory, and synthetic one is important in the initiation and progression of atherosclerosis. This change is controlled by mitogen-activated protein kinase pathways and mediated by phosphorylation of connexin 43 protein, which may represent another future nonlipid target to prevent atherosclerosis and restenosis.⁵⁸ Smooth muscle cells, through foam cell transformation and senescence, may later undergo apoptosis within the necrotic core.

Macrophages participate in cross-talk with a panoply of amplifying proinflammatory cytokines that affect endothelial, smooth muscle, and immune cells, as well as coagulation mechanisms. Oxidized LDL and a variety of oxidized phospholipids and other specific oxidative epitopes are recognized by ligands for pattern recognition receptors of the innate immune system, such as toll-like receptors (TLRs) and C-reactive protein. In addition to smooth muscle cells that migrate to the intima initially or arise from progenitor cells, continuing accumulation of lipid-laden macrophages increases the size of atheroma as they remodel into the vulnerable plaque phenotype, ie, the thin fibrous cap overlying a necrotic, lipid-rich core. Disappearance of smooth muscle cells, which provide fibrous collagen for plaque stabilization, may contribute to plaque vulnerability. Oxidized phospholipids (oxysterols) and nonesterified free cholesterol induce stress in the endoplasmic reticulum, leading to defective phagocytic clearance of dead lesional macrophages and plaque necrosis.⁵⁹

Ongoing amplification of cytokine expression and reactive oxygen species by macrophages and mature foam cells induced by lipid accumulation, alterations in proinflammatory gene expression, and networked immune reactions, including presentation of antigens by dendritic cells to involve the adaptive immune system, continue during plaque development.^{60,61} Pattern recognition receptors, together with cellular and humoral components, play crucial and ongoing roles in the maturation of atheroma and remodeling of plaques, including destabilization, erosion, rupture, and thrombogenicity of the contents.⁶² In general, maneuvers that decrease inflammation and those that interrupt TLR signaling reduce lesion size. Eventually the activity of proteinases secreted by macrophages and foam cells degrades sufficient collagen and matrix to permit lesion rupture, exposing the prothrombotic contents to the intravascular space.

Suppressing recruitment of monocytes or facilitating emigration of macrophages from atherosclerotic lesions would be expected to decrease plaque volume.⁶³ Progression or regression of such lesions depends on a balance between monocyte recruitment and emigration of macrophages.^{64,65} Netrin-1, a molecule which guides movement of neurons, has immunomodulatory properties because of its ability to disrupt Rac1 signaling and organization of the actin cytoskeleton. Secreted by macrophage foam cells within plaques, netrin-1 inhibits foam cell migration, and is also involved in chemoattraction of smooth muscle cells.⁶⁶ Impeding expression of netrin-1 and related molecules which control movement of macrophages offers additional therapeutic targets, which are under investigation.^{66,67}

A recent pivotal meta-analysis⁶⁸ and Mendelian randomization study⁶⁹ support a causative role for interleukin-6 in producing coronary heart disease. However, despite strong preclinical evidence that inflammation drives atherosclerosis, suggestions from experience with anti-inflammatory agents, such as statins, aspirin, and colchicine, and the well-studied association between C-reactive protein levels and outcomes, inflammation reduction trials providing direct evidence that targeting inflammation per se produces benefits have not been done. Canakinumab is a high-affinity monoclonal antihuman interleukin-1 β antibody that lowers levels of interleukin-1 β and C-reactive protein without causing significant changes in LDL or HDL cholesterol. Interleukin-1 β , a proinflammatory cytokine released by activated macrophages as a precursor, is subsequently changed to an active form by caspase-1, an enzyme overexpressed in plaques.^{70,71} For these reasons, canakinumab is an appropriate agent for studying the effect of inhibition of inflammation upon cardiovascular outcomes. CANTOS (the Canakinumab Anti-inflammatory Thrombosis Outcomes Study) is a double-blind, multinational investigation enrolling 17,200 participants and investigating the effects of subcutaneous canakinumab in stable secondary prevention patients with high cardiovascular risk and persistent C-reactive protein >2 mg/L despite conventional care, with a primary endpoint of the composite of cardiovascular death, nonfatal myocardial infarction, and stroke.⁷² A report of a Phase IIB trial involving 556 participants with controlled type 2 diabetes and high cardiovascular risk randomized to monthly canakinumab doses of 5 mg, 15 mg, 50 mg, or 150 mg and then followed for 4 months has recently been released.⁷³ Significant reductions in C-reactive protein, interleukin-6, and fibrinogen were found in the treated group in the absence of limiting adverse effects. CIRT (the Cardiovascular

Inflammation Reduction Trial) is a randomized clinical investigation of the effects of low-dose methotrexate on the primary endpoint of recurrent myocardial infarction, stroke, and cardiovascular death rates in stable patients with type 2 diabetes or metabolic syndrome who have sustained a myocardial infarction within the previous 5 years. This is a 4-year Phase III study funded by the National Heart, Lung, and Blood Institute, and plans to enroll 7,000 participants.^{74–76} The results of CANTOS and CIRT are expected to shed light on the clinical potential of the “inflammation” hypothesis.

MicroRNAs are highly conserved, small, noncoding, single-stranded RNAs, about 18–22 nucleotides in length, that regulate gene expression via transcriptional degradation and sequestration, and translational activation or inhibition. Multiple microRNAs play roles at many of the steps in atherogenesis mentioned above, including nitric oxide synthase activity and endothelial function, adhesion molecule expression and monocyte recruitment, smooth muscle cell proliferation, macrophage differentiation and cytokine release, modulation of macrophage cholesterol efflux, regulation of vascular inflammation, plaque progression and disruption, autophagy and apoptosis, and promotion of neoangiogenesis.^{77,78} MicroRNAs also regulate a number of processes and molecules involved in generating general cardiovascular risk. Examples are obesity, insulin resistance, diabetes, aging, stem cell progenitors, peroxisome proliferator-activated receptors, and leptin. In the future, microRNA profiles may serve as markers in assessment, and eventually provide additional targets for intervention.

Finally, modulation of not only innate but also adaptive immunity offers future therapeutic potential. The innate immune system is involved in the recruitment and entry of monocytes into atherosclerotic lesions, followed by maturation into macrophages and CD11c⁺ cells with dendritic morphology and properties, in addition to a heterogeneous population of other dendritic cells. Dendritic cells are potent antigen-presenting cells. Toll-like receptors connect the innate and adaptive immune systems by stimulating dendritic cells to present antigens to T cells;^{79,80} these processes are important in the initiation and progression of coronary heart disease, including thrombotic complications.⁸¹ Dendritic cells embedded in the arterial wall perform surveillance and induce tolerance to autoantigens by silencing T cell activation. Mature dendritic cells may accumulate physically in relation to T cells within atherosclerotic lesions.⁸² Some types of activated T cells participate in further proinflammatory and proatherogenic signaling, whereas others are cardioprotective.^{83,84} In fact, assessing the activity of genes in the TLR/

interleukin-1 receptor signaling pathway may reflect early inflammatory activity in the preclinical stages of coronary heart disease, and prove to be useful biomarkers of risk in individuals considered to be at low risk using traditional global scoring.⁸⁴ Regulatory T cells play a central role in controlling immune responses by adjusting peripheral tolerance. In this context, modified LDL cholesterol may be viewed as an autoantigen, given that altered fragments of apolipoprotein B100 (ApoB-100) may act as antigenic epitopes leading to T cell activation. Up to 10% of T cells from human plaques recognize oxidized LDL.⁸⁵ Immunization against a specific isotype of T cell receptor involved in such responses impedes atherosclerosis. Such modification of dendritic cells so that they become tolerant to stimulation by ApoB-100 fragments inhibits proatherogenic activation of effector T cells, thereby favoring the anti-inflammatory and atheroprotective actions of regulatory T cells, has been demonstrated in hypercholesterolemic mice. Immunization with self-antigens forms the basis of the so-called dendritic cell vaccine approaches to impede atherosclerosis by promoting regulatory T cell activity.^{86–88}

Regulatory T cells expressing the forkhead/winged helix transcription factor (Foxp3⁺) control the development of atherosclerosis in mice,⁸⁹ along with a significant role of the anti-inflammatory cytokine, interleukin-10. Preventing depletion of Foxp3⁺ regulatory T cells may protect against atherosclerosis, opening up another therapeutic target for exploration.⁹⁰ In humans, low levels of regulatory T cells (CD4⁺FoxP3⁺) were associated with enhanced proinflammatory cytokine expression by activated monocytes and a greater risk of acute myocardial infarction over a 15-year study period.⁹¹ Studies involving regulatory T cells in humans, rather than mice, are somewhat hampered by technical difficulties in their identification. Moreover, the ability of regulatory T cells to inhibit progression of atherosclerosis may wane over time, and they may even differentiate into proinflammatory T17 cells.⁹² The reader is referred to recent discussions for details.^{93,94}

Although activation of the innate and adaptive immune systems contributes to plaque instability in acute coronary syndrome, inflammation does not explain pathogenesis of this syndrome in all such patients. There are many causes of coronary instability in acute coronary syndrome as compared with stable ischemic heart disease, and precise differences between the two syndromes remain unclear.⁹⁵

In conclusion, the inflammatory component of atherogenesis may help to explain a portion of residual risk, plays an important continuing role in the development of

atherosclerotic lesions and complications, and provides a number of potential targets for therapy. Several proteins with potential roles in adjusting inflammatory responses include the bromodomain and extraterminal proteins controlling gene expression and others operating at different levels.⁹⁶

Genetic contribution to residual risk

Family history is important in cardiovascular risk, and epidemiologic evidence suggests about half of the risk for coronary heart disease is heritable. The capability of genome-wide association screens has greatly extended the capability of the former single candidate gene approach, and many significant single nucleotide polymorphism-trait associations have been made for traditional risk factors^{97,98} and unrelated coronary heart disease susceptibility variants.⁹⁹ However, all such known risk variants together account for but a fraction of the heritability of well-established risk factors and cardiovascular disease.¹⁰⁰ Genome-wide association screens have now identified 36 significant risk variants for coronary heart disease, but the mechanisms of action are known for only 13 of them.¹⁰¹ The first variant predisposing to coronary heart disease, on the short arm of chromosome 9, ie, locus 9p21.3, for instance, may account for a 20%–40% increased risk of coronary heart disease.^{102,103} The 9p21 variant is found in approximately 75% of persons worldwide, but not in African-Americans.

Several polymorphisms relating to cholesterol metabolism, response to statins, and adverse effects are well described. Genetic variation, including differences in statin responsiveness, adverse reactions, and other processes modulating risk, accounts for some of what is considered to be residual risk.¹⁰⁴ Although genetic variants of cholesteryl ester transfer protein (CETP) are fairly common, a meta-analysis indicated that CETP genotypes have a weak inverse association with coronary risk.¹⁰⁵

Genome-wide association screens have identified approximately 95 distinct loci concerned with LDL cholesterol, HDL cholesterol, and/or triglycerides, with 65% previously considered not to be associated with lipoproteins.¹⁰⁶ The number of permutations for a single nucleotide polymorphism may be large (over 40 variants in ApoA-I are known), but their significance remains elusive. Heterogeneity in statin responsiveness has attracted considerable attention. However, additional microarray-derived associations exist with nonlipid risk factors, such as gene expression in adipose, hepatic, and β cell tissues in obesity and diabetes¹⁰⁷ or those relating to the origins of hypertension.¹⁰⁸

There is increasing appreciation for wide interindividual variation between plasma levels of rosuvastatin and atorvastatin associated with differences in uptake and efflux transporter polymorphisms, even with consistent dosing. In addition, the search continues for additional loci, such as the gene that encodes the rate-limiting enzyme in creatine synthesis, glycine amidinotransferase, that might assist in predicting statin myopathy.

The failure to identify a robust, underlying cohesive relationship between genetic risk variants and cardiovascular disease-related phenotypes may simply reflect inadequate gene expression databases and as yet unidentified biochemical pathways. Genetic variants predisposing to coronary heart disease that do not act through known risk factors provide a blueprint to explore such DNA regions and will hopefully lead to discovery of additional molecular pathways. Undoubtedly, some of these will uncover new mechanisms contributing to residual risk.

Endothelial progenitor cells, microparticles, and risk variation

Endothelial dysfunction is an early event in cardiovascular and related diseases, and various functional markers of endothelial impairment may correlate with extent of disease and/or predict morbidity and mortality.^{109–111} Methods commonly used to assess endothelial function include brachial flow-mediated vasodilation, easily performed pulse amplitude tonometry in the small arterial bed, and measurement of biochemical markers. Less attention is given to cellular markers of vascular health, ie, endothelial progenitor cells, circulating endothelial cells, and microparticles. Endothelial progenitor cells are immature small (10–15 μm) precursor cells that originate in the bone marrow and are able to differentiate into endothelial cells, form true endothelial tubes in vitro, and repair and regenerate the endothelium during re-endothelialization and neovascularization in vivo. After endothelial injury, circulating endothelial progenitor cells home to these sites and help restore endothelial integrity and functional homeostasis. In laboratory animals, endothelial progenitor cells may prevent atherosclerosis even in the face of hypercholesterolemia¹¹² and are capable of increasing endothelial nitric oxide synthase activity.¹¹³

Given that endothelial progenitor cells participate in vascular repair, they not only reflect stress and damage, but may also directly influence risk. The endothelial progenitor cell population falls with aging, as do stem cell numbers generally, and are also less abundant in association with traditional risk factors, ie, smoking, hypertension, dyslipidemia,

diabetes, physical inactivity, and obesity.¹¹⁴ Lowering of endothelial progenitor cell numbers and/or impaired endothelial progenitor cell activity is believed to occur as early in the atherosclerotic process as impaired nitric oxide availability or production of cell adhesion markers. The number of endothelial progenitor cells is low in patients with stable coronary heart disease, and their levels predict the risk of an initial MCVE and/or death from cardiovascular causes.¹¹⁵ Evidence also connects endothelial progenitor cell reduction and inflammation, insulin resistance, microalbuminuria, and hyperhomocysteinemia. Antihypertensive, antidiabetic, and statin therapy may all increase endothelial progenitor cell numbers.¹¹⁶ Likewise, improvement in risk factors through lifestyle changes, ie, nutrition, exercise, and weight loss, are accompanied by a rise in circulating endothelial progenitor cell activity.^{117,118}

During acute events, including acute coronary syndrome and stroke, endothelial progenitor cells are mobilized from the bone marrow and their numbers rise. The vigor of endothelial progenitor cell release is associated with outcomes (volume of infarcted tissue, left ventricular function, neurologic residua), and the prevailing view is that the more endothelial progenitor cells available to repair an ischemic insult, the better. Further, when pathology exists that may depress endothelial progenitor cell mobilization, the prognosis may worsen. Diabetes¹¹⁹ and a high risk factor burden may be such conditions. In heart failure, changes in endothelial progenitor cell number may be biphasic, being elevated during the early phases but depressed during advanced stages.

Circulating membrane-shed microparticles, defined by their size (diameter 0.1–1.0 μm) and content, may be found in healthy subjects, although their numbers are considered to be markers of cell damage, arise not only from activated, injured, or apoptotic endothelial cell membranes, but also from platelets, leukocytes, smooth muscle cells, and erythrocytes. Many microparticles directly impair protective actions of endothelium, in part through promotion of adhesion factor expression, monocyte migration, and reduced nitric oxide availability, and likely participate in amplifying atherogenic processes.^{120,121} The origin of the microparticles may influence the specifics. For instance, microparticles from monocytes activate endothelial cells through interleukin-1 β . Microparticles of endothelial, platelet, and leukocyte origin most closely reflect endothelial dysfunction, and are also biomarkers of disease progression.¹²² C-reactive protein induces release of both circulating endothelial cells and endothelial microparticles in vivo, in association with endothelial dysfunction, mediated by endothelial nitric oxide synthase

uncoupling and nitric oxide deficiency, and subsequent polarization of macrophages to a proinflammatory phenotype.¹²³ In particular, microvesicle formation may be induced by nonesterified cholesterol-laden cells, especially monocytes, activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), and increase intercellular adhesion molecule 1 levels significantly.¹²⁴ These relationships are important because the endothelium may play a major role in clearing microparticles from the circulation generally. Microparticles within plaques further their progression by increasing inflammation, promoting apoptosis, stimulating angiogenesis (which increases lesion vulnerability), interfering with endothelial progenitor cell repair, and/or by directly raising the thrombogenicity of lesion contents.^{120,121} Circulating microparticles derived from endothelial cells and platelets may contain phenotypic markers and functional enzymes found in their respective cells of origin, including endothelial nitric oxide synthase, which can reflect endothelial dysfunction evident in the parent cells. The significance of these findings awaits further study.¹²⁵

Considerable work is yet to be done regarding definitions, measurement, standardization, and assessment of the clinical utility of endothelial progenitor cell dynamics. Further research may yield additional details concerning mechanisms of endothelial function and present unique opportunities for intervention through cellular repair.

HDL biology, quantity, quality, and residual risk

HDL and reverse cholesterol transport

As mentioned, both low levels of HDL cholesterol¹³² and high levels of triglycerides¹²⁶ are associated with a higher risk of MCVE in untreated and statin-treated patients, leading to the belief that HDL is antiatherogenic and that triglycerides contribute to risk. Consistent with these hypotheses, low triglyceride levels in statin-treated patients predict reduced risk.¹²⁷ When LDL cholesterol is controlled, the odds of coronary heart disease fall by about 40% per 0.194 mmol/L (7.5 mg/dL) rise in HDL cholesterol, and the odds of coronary heart disease increase by approximately 20% per 0.260 mmol/L (23 mg/dL) rise in triglyceride levels.¹²⁸ This translates to a fall in MCVE by about 1.1% for each 0.026 mmol/L (1 mg/dL) rise in HDL cholesterol when LDL cholesterol is <1.81 mmol/L (70 mg/dL).¹²⁹ The inverse association between MCVE and low HDL cholesterol is not eliminated by aggressive statin therapy. In order to stop plaque progression or effect regression of atheroma, a meta-analysis using intravascular ultrasonography suggests that

both an LDL cholesterol <2.262 mmol/L (87.5 mg/dL) and a rise in HDL cholesterol of >7.5% are necessary.¹³⁰

A low level of HDL cholesterol is a pernicious finding in high risk patients, especially diabetics. In the Lipid Research Clinics Prevalence Study¹³¹ patients were classified according to extent of cardiovascular disease and followed for an average of 10.1 years. Comparing cardiovascular risk in patients with and without coronary heart disease, low HDL cholesterol added risk for cardiovascular mortality in every tertile. In those with the lowest levels of HDL cholesterol, there was a 12-fold increase in mortality risk for those with coronary heart disease compared with those without coronary heart disease.

The best known function of HDL is its role in reverse cholesterol transport, which begins when the lipid-void ApoA-I or pre- β HDL molecule, secreted by the liver and intestine, receives cholesterol from macrophage ATP-binding cassette transporter A-1 in the arterial wall. ApoA-I constitutes about 75% of the protein content of HDL cholesterol, which is a cofactor for the lecithin cholesterol acyltransferase reaction and participates in cholesterol release back to the liver. The resulting nascent “discoid” pre- β HDL begins remodeling as free cholesterol is esterified by lecithin cholesterol acyltransferase into cholesteryl esters, which are incorporated into the molecule to form more mature α -HDL particles. ATP-binding cassette transporter G-1 transporter facilitates cholesterol efflux to more mature HDL particles. Esterification of cholesterol raises the gradient driving cholesterol egress from macrophages, prevents rediffusion, and promotes further removal of cholesterol from the vascular wall, but is not essential for reverse cholesterol transport. As the particle evolves, additional lipophilic cholesteryl ester moves to the lipid core, and a spherical shape is assumed by the ensuing forms, known as HDL3 and the larger HDL2. α -HDL particles may then either transfer cholesteryl ester to ApoB-containing lipoproteins, eg, very-low-density lipoprotein (VLDL) and LDL, mediated by CETP, or to the liver through the action of scavenger receptor class B type 1. CETP, a glycoprotein, facilitates the exchange of neutral lipids, cholesteryl esters in HDL particles, for triglycerides in ApoB-containing lipoproteins. The ability of HDL to store cholesterol is limited, and hence maintenance of free cholesterol efflux from macrophages is a function of its capacity to transfer this cholesterol in later steps to LDL and VLDL. Over 70% of cholesterol is returned to the liver through hepatic catabolism of ApoB-containing lipoproteins. However, direct transfer of lipids out of HDL with the assistance of scavenger receptor class B type 1 occurs in the liver to complete the reverse cholesterol transport cycle. Experimental deletion of the

macrophage transporters, ATP-binding cassette transporter A-1 and ATP-binding cassette transporter G-1, raises the lipid content of macrophages and accelerates atherogenesis, in part by independent cytokine-induced monocyte and neutrophil production within plaques.

Normally, reverse cholesterol transport involves removal of free cholesterol from the macrophage to HDL in the extracellular space, esterification to cholesteryl ester in an irreversible, energy-consuming step catalyzed by lecithin cholesterol acyltransferase, and transport in HDL, transfer to an ApoB-containing lipid via CETP or delipidation of HDL cholesterol catalyzed by hepatic scavenger receptor class B type 1 directly. Through either pathway, cholesterol is returned to the liver and may be eliminated from the body as fecal sterols. The delipidated HDL particle is released into the blood to begin another cycle. Interruption of the transfer mediated by CETP inhibition is accompanied by a rise in HDL cholesterol, and with some agents, a fall in LDL cholesterol. However, since CETP inhibition produces an increase in large HDL, which is not as efficient in reverse cholesterol transport as smaller HDL. As a result, there is considerable speculation about whether the HDL associated with CETP inhibition would be functional, and this is an issue yet to be resolved with each such agent.

Raising HDL cholesterol, based on the assumption that it is a good surrogate for cholesterol efflux out of macrophages in arterial walls, a process correlated with reduction in MCVE, has been a major pursuit in reduction of residual risk.^{132,133} This goal is supported by impressive data from epidemiologic and preclinical studies. Promoting cholesterol efflux from macrophages by raising HDL cholesterol would be expected to improve endothelial function and lower levels of vascular cell adhesion molecule 1 and intercellular adhesion molecule 1, raise endothelial progenitor cell numbers, reduce oxidative stress, LDL oxidation and subendothelial oxidized LDL retention, suppress macrophage-related inflammatory signaling, and slow formation of necrotic cores within plaques. The assumption and hope has been that the larger numbers of HDL particles would be relatively empty, and be able to transport more cholesterol away from the arterial wall.

On the other hand, the amount of cholesterol uploaded by peripheral macrophages during reverse cholesterol transport and contributing to the total HDL cholesterol pool is small, being approximately 3%–5% of the total HDL cholesterol mass.¹³⁴ In an animal model using ATP-binding cassette transporter A-1 knockout mice, it has been shown that little HDL cholesterol in the plasma results from tissue macrophage efflux,¹³⁵ so the blood levels do not change.

The bulk of cholesterol in HDL cholesterol is derived from ATP-binding cassette transporter A-1 activity in the liver and intestine, not from reverse cholesterol transport in peripheral tissue. Without an available method to measure macrophage cholesterol efflux in vivo,¹³⁴ details about the protective contribution of this particular HDL function remain unclear.¹³⁶ A promising technique for the future is use of labeling with an alternative heavy water, (²H₂O), to measure turnover of both HDL cholesterol and ApoA-I flux in vivo, study effects of pharmacological agents and genetics upon HDL flux and macrophage cholesterol efflux.

Further, there are several well-known examples in which HDL cholesterol levels are raised in the absence of atheroprotection. When hepatic ATP-binding cassette transporter A-1 is overexpressed in an animal model, HDL cholesterol levels rise, but HDL function is impaired and atherosclerosis is accelerated.¹³⁷ Patients with genetic lecithin cholesterol acyltransferase deficiency or mutations within the *ApoA-I* gene resulting in hypofunction of ApoA-I secretion have marked HDL cholesterol deficiency, but development of atherosclerosis is variable.¹³⁸ CETP deficiency from mutations in the *CETP* gene also increase HDL cholesterol, but protection against atherosclerosis is irregular. Raising HDL cholesterol with torcetrapib, estrogen, or fibrates need not improve outcomes. These data suggest that cholesterol may return to the liver without involving all the usual steps in reverse cholesterol transport, and/or there may be dissociation between HDL cholesterol concentrations and atherogenic protection.

HDL composition and additional functions

HDL cholesterol is a complex mixture of diverse particles with differing composition and function. Each HDL particle carries between two and five molecules of ApoA-I, and therefore the level of ApoA-I does not accurately reflect the number of HDL particles (HDL-Ps). Further, each HDL-P potentially carries microRNAs (each regulating >50% of genes and involving approximately 100 target sites), over 80 proteins, and hundreds of lipid moieties, with many molecules retaining their intrinsic biological activities in non-lipid processes, particularly antioxidant and antithrombotic properties. A large number are concerned with inflammation and the complement system. Such observations direct attention to the pleiotropic properties of HDL, and together with the material discussed below, there is increasing awareness that HDL quality may be more important than HDL quantity. This view may help explain why no large-scale randomized trial has established that raising HDL cholesterol

levels improves hard cardiovascular outcomes. The relationship between alterations in HDL and functional changes is also likely to be complex. Testosterone therapy in hypogonadal men, for example, changes the protein composition of HDL together with significant increases in HDL-associated paraoxonase-1, which is unaccompanied by improvement in HDL-mediated cholesterol efflux.

Functions of HDL include not only roles in reverse cholesterol transport, chiefly involving ApoA-I and mediated by ATP-binding cassette transporter A-1, but also include anti-inflammatory, antioxidant, antithrombotic, and antiapoptotic properties.^{139,140} Many of these actions are mediated or modified by the large array of lipid and protein cargo carried within HDL particles, including enzymes, eg, paraoxonases and glutathione peroxidase.¹⁴¹ Among other antiatherogenic properties of HDL are roles in the innate immune system and promotion of endothelial progenitor cell proliferation, recruitment, and “tube” formation, the net effect of which is improved repair, re-endothelialization, and enhanced endothelial function.¹⁴² HDL cholesterol as usually measured provides only the weight/deciliter of a pool of heterogeneous molecules with differing density, charge, and composition, approximately half protein and half lipid. HDL may remove some products of lipid oxidation, and the inherent antioxidant properties of ApoA-I, antioxidant enzymes, and reducing sulfhydryl groups on cysteine moieties can clear oxidized products. In doing so, they may prevent LDL oxidation, render it less toxic, and reduce associated inflammatory responses.

HDL-associated paraoxonases (PON1 and PON3) inhibit lipid oxidation and reduce cholesterol synthesis, slow LDL aggregation and oxidized LDL formation, suppress monocyte-to-macrophage differentiation, and promote cholesterol efflux from macrophages (PON1).¹⁴³ Importantly, PON1 activity is reduced in patients consuming a high fat/high cholesterol diet, smokers, those with coronary heart disease, type 2 diabetes, obesity, rheumatoid arthritis, hemodialysis, during old age, an acute phase response, or molecularly by exposure to oxidized LDL or glutathionylation, which are all conditions united by high oxidative or nitrosative stress and lipid peroxidation with oxidation of the free sulfhydryl group at Cys on PON1.¹⁴³ PON1 activity may be induced by a Mediterranean diet meal, or certain dietary polyphenols, in part through signaling involving peroxisome proliferator-activated receptor gamma (PPAR-γ).

HDL is the major lipoprotein carrier of plasma F2 isoprostanes, a product of lipid oxidation that is used to monitor oxidative stress. HDL exerts anti-inflammatory actions to

lower expression of adhesion molecules and atherogenic cytokines. Protective HDL also improves endothelial function directly by stimulation of endothelial nitric oxide synthase and nitric oxide-mediated vasodilation via the action of endothelial scavenger receptor class B type 1^{144,145} and additional mechanisms other than improved cholesterol efflux.¹⁴⁶ HDL is the major carrier of sphingosine-1-phosphate in plasma; liberation of this molecule by endothelial lipase mediates Akt kinase and nitric oxide synthase activation in endothelial cells, promoting endothelial cell migration, tube formation, and angiogenesis.

Antithrombotic actions of HDL include indirect inhibition of platelet activation and aggregation, raised production of prostacyclin, downregulation of thrombin generation via the protein C pathway, lowering expression of selectins and tissue factor, and promotion of fibrinolysis. HDL improves glucose metabolism, both by raising insulin sensitivity and protecting β cells from cholesterol-induced β cell dysfunction, stress-induced apoptosis, and islet inflammation.¹⁴⁷ Finally, another recently described antiatherogenic action is interference of HDL2 with initial entrapment of LDL to form insoluble LDL-proteoglycan associations, an initial step in the arterial intima leading to retention of LDL in the arterial wall.¹⁴⁸ Since the larger HDL particles are more effective in such binding, and small HDL sizes are typical in diabetics, greater LDL entrapment in the absence of this action of large HDL may contribute to increased cardiovascular risk.

HDL has a greater role in modulating inflammation than the relationships with lipid metabolism discussed thus far. Only one third of the HDL proteome is related to lipid transport; the remainder is concerned with acute phase reactions, complement, and protease inhibitors, which link HDL to inflammation, immunity, and coagulation. During acute phase reactions, the composition of HDL changes significantly, ie, the amount of serum amyloid A associated with HDL rises, ApoA-I levels and PON activity decrease by approximately 70%, and the protective effect against LDL oxidation falls.¹⁴⁹ Serum amyloid A-enriched HDL has increased affinity for vascular proteoglycans, leading to retention in the arterial intima and exposure to oxidation and modification.

HDL is a highly conserved lipoprotein in many species, has antibacterial and antiviral properties, and limits toxicity of various microbial products, including lipopolysaccharide, enterohemolysin, and lipoteichoic acid. Several lines of evidence suggest HDL evolved as part of the innate immune system. When macrophages are exposed to lipopolysaccharide, a well-known TLR ligand, ATP-binding cassette

transporter A-1 and ATP-binding cassette transporter G-1 transporters are inhibited and macrophage cholesterol efflux is impaired.¹⁵⁰ In patients with sepsis, neutralization of lipopolysaccharides by ApoA-I is a central defense mechanism, but is accompanied by a 73% reduction of macrophage efflux to remodeled HDL.

Healthy HDL also lowers expression of chemoattractants, such as monocyte chemoattractant protein which recruits T cells, monocytes, and dendritic cells to inflammatory lesions. HDL is involved in humoral innate immunity through the complement system and expression of pentraxin 3, but also with antigen presentation in B cells, macrophages, and dendritic cells.¹⁵¹

Cytokines regulate HDL function in part through physical modification,¹⁵² perhaps constituting one limb of substantial cross-talk between reverse cholesterol transport and inflammatory pathways in which TLRs and HDL participate.¹⁵³ Healthy HDL attenuates some damaging effects of the complement system, inhibits antigen presentation-mediated T cell activation, and specifically lowers the production of proinflammatory cytokines induced by T cell contact. Biochemical details of reactions involved in HDL biology may be found elsewhere.^{154–157}

Transfer of cholesterol by ATP-binding cassette transporters to HDL not only assists with cholesterol metabolism, but is linked to additional signaling mediated by genetic anti-inflammatory programs. The structural platform for this link is provided by “lipid rafts”, ie, microdomains in membranes with high concentrations of cholesterol, sphingolipids, and proteins responsible for signaling, particularly through T cell receptors. As HDL removes cholesterol from rafts, signaling is disrupted. Failure of raft integrity impairs immune cell activation, antigen presentation, T cell activation, expression of TLRs, and quells inflammation. Evidence for this schema has been recently detailed.¹⁵¹ Direct support for this sequence of events has been provided by Wang et al¹⁵⁸ using murine culture cells. Their data were consistent with the view that cholesterol efflux by HDL interrupted T cell activation, which was restored by cholesterol repletion. Interestingly, lowered cholesterol content in lipid rafts and modification of signaling in multiple transduction pathways has been proposed for liver X receptor effects other than ATP-binding cassette transporter regulation. Liver X receptors, members of the nuclear receptor family of transcription factors, are cholesterol-sensing whole-body regulators of cholesterol metabolism with antiatherosclerotic, anti-inflammatory, antiproliferative, antidiabetic, and prosurvival actions.^{159,160} Not only do these regulators induce genes involved in reverse

cholesterol transport, but also coordinate suppression of proinflammatory genes in response to bacterial, lipopolysaccharide, interleukin-1 β , or tumor necrosis factor- α stimulation. In essence, activation of TLR-4 by these stimuli reduces liver X receptor-dependent gene transcription and macrophage cholesterol efflux. Pharmacologic activation of endothelial liver X receptors inhibits angiogenesis, mediated through cholesterol-dependent vascular endothelial growth factor receptor-2 signaling.¹⁶¹ Interference with lipid raft function in endothelial cells, rich in such domains and unusually sensitive to cholesterol levels, is the likely mechanism as well. In this context, cholesterol depletion in membranes changes their mechanical properties, membrane-cytoskeleton adhesion, and leads to disappearance of caveolae, whereas cholesterol repletion may induce formation of caveolae. High-resolution imaging mass spectrometry confirms that altering cell cholesterol content changes cell function and the number and organization of lipid rafts, which are also actin-dependent. The dominant atherogenic consequences of cholesterol removal may not always be predictable; doing so in an endothelial cell may impair biomechanics, but in a macrophage may inhibit polarization, migration, and foam cell formation, depending upon experimental conditions.^{57,162–168}

Relationship between changes in HDL and function: importance of HDL quality

As the composition of HDL changes, molecular remodeling may be accompanied by variations in function that compromise the molecule's ability to protect against atherosclerosis. Generally, HDL3, containing less cholesterol and phospholipids, more protein, and hence greater density, has more potent anti-inflammatory, antioxidant, and antithrombotic actions than the HDL2 fraction. HDL3 provides greater protection than does HDL2 against LDL oxidation in several *in vitro* models. Partial explanations may lie with the power of HDL3 to efflux cholesterol from lipid-laden cells, and ability of the protein cargo to contend with the burden of toxic oxidized lipid components associated with the particle. Complicating matters further than the differing antiatherogenicity between HDL classes,¹⁶⁸ the possibility that different functions of HDL may be more important under one set of conditions than another cannot be dismissed. However, HDL-P appears to be inversely associated with atherosclerotic risk and coronary heart disease independently of both atherogenic lipoprotein levels and its own cholesterol content, and may be ultimately shown to closely reflect residual risk.¹⁶⁹ Nonetheless, there is currently insufficient evidence to use HDL subclasses, nor any practical method of assessing function, as a basis for clinical decisions.

HDL from the plasma of patients with stable coronary heart disease or acute coronary syndrome, carrying a protein cargo distinct from that of healthy subjects, can become proinflammatory regardless of the plasma LDL cholesterol concentration.^{154,170} Such HDL-proteome remodeled “dysfunctional” HDL from these patients cannot stimulate endothelial repair, inhibit secretion of vascular cell adhesion molecule 1, suppress activation of NF- κ B, or reduce expression of LDL-induced endothelial monocyte chemoattractant protein and consequent monocyte adhesion, and may stimulate endothelial proapoptotic signaling pathways.¹⁷¹ The vasoprotective actions of HDL are also lost in patients with chronic kidney disease, which may be associated with a remodeled HDL-proteome cargo containing higher amounts of serum amyloid A1, lipoprotein-associated phospholipase A2, apolipoprotein C-III (ApoC-III), lysophospholipids, triglycerides, and albumin, and a lower content of phospholipid.¹⁷² Such changes impair the ability of “uremic HDL” to effect macrophage cholesterol efflux (see below). Proinflammatory HDL is also found during acute phase reactions, in association with suppressed activity of PON enzymes, and in patients with autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. Reduced HDL cholesterol levels rise predictably in a variety of autoimmune diseases after anti-inflammatory treatment is started.

ApoC-III, a small proinflammatory protein upregulated in insulin resistance syndromes due to loss of insulin-mediated, transcription factor-mediated, and farnesoid X receptor-mediated inhibition of ApoC-III expression, and partly driven by excess glucose or free fatty acids,¹⁷³ may similarly render HDL dysfunctional.⁸⁸ ApoC-III is a regulator of plasma triglycerides, and is associated with high triglyceride levels, metabolic syndrome, and type 2 diabetes. ApoC-III is capable of promoting assembly and secretion of VLDLs in the liver, and enhances the atherogenicity of triglyceride-rich lipoproteins, but also increases endogenous thrombin generation.¹⁷⁴ Serum levels of ApoC-III are strong predictors of cardiovascular risk, even after adjusting for classical lipid risk factors.^{175,176} In addition, however, ApoC-III is but one of the atherogenic molecules that may be acquired by HDL as it is secreted in the liver or intestine, or by transfer from VLDL, and its importance is increasingly recognized.^{177–179} Current evidence suggests that ApoC-III redistributes in uncertain ways among lipoproteins, involving: slow receptor-mediated uptake of VLDL, LDL, and intermediate-density lipoprotein by the liver; promotion of hepatic synthesis and release of VLDL; inhibition of hepatic and lipoprotein lipases; effects

on scavenger receptor class B type 1 and ATP-binding cassette transporter A-1; activation of vascular endothelial cells and increasing expression of adhesion molecules, linking dyslipidemia and endothelial dysfunction; release of monocyte chemoattractant protein and interleukin-6 using TLR-2 in adipocytes; and the pathogenesis of atherogenic dyslipidemia.¹⁸⁰ Recently, when HDL having opposing associations with risk of coronary heart disease was analyzed, HDL cholesterol containing ApoC-III was found to be less protective than HDL cholesterol not containing ApoC-III.¹⁷⁸ HDL cholesterol may be divided into two populations, a major one lacking surface ApoC-III and associated with a better prognosis, and a smaller one (about 13%) containing ApoC-III and associated with higher risk. Thus, although HDL molecules are dynamically heterogeneous, it may be possible to identify and measure their atherogenic constituents, which could be potentially useful in stratification and perhaps even future therapy. Indeed, ApoC-III-induced monocyte adhesion to endothelial cells in coronary arteries, mediated by NF- κ B pathways, were suppressed by pretreatment with statin drugs, with lipophilic statins demonstrating a relatively greater effect. ApoC-III appears to be an attractive therapeutic target,¹⁷⁹ and interfering with ApoC-III offers the advantage of intervention at the level of endothelial dysfunction, monocyte recruitment, and NF- κ B activation early in the development of atherosclerotic lesions, again supporting a dual lipid-lowering and anti-inflammatory approach to therapy. Antisense nucleotides targeting ApoC-III expression have been used successfully in humans and are under active study.

Diabetes is another disease in which several structural modifications may occur and impair HDL function.¹⁸¹ Glycation of HDL cholesterol shortens its half-life, attenuates antioxidative properties, increases monocyte adhesion to endothelium after exposure to oxidized LDL, and decreases the effectiveness of PON1 in reducing synthesis of monocyte chemoattractant protein.¹⁸² The coexistence of type 2 diabetes and coronary heart disease can reduce PON1 activity by up to 40%, seriously lowering the capacity of HDL to deter LDL oxidation.

Deleterious changes in lipoprotein metabolism develop in most patients with chronic kidney disease, often during the asymptomatic stages. Hypertriglyceridemia and diminished catabolism of lipoproteins containing ApoB are common, with increased amounts of ApoC-III and low HDL cholesterol levels containing lower amounts of ApoA-I, ApoA-II, cholesterol, and phospholipid.¹⁸³ Typically, ApoB (both ApoB-48 and ApoB-100), small dense LDL, and lipoprotein(a) levels are elevated, but LDL cho-

lesterol levels are not usually increased,¹⁸⁴ although higher LDL cholesterol concentrations may add to risk. ApoC-III contributes to the lower clearance of triglyceride-rich lipoproteins, while inhibition of lipoprotein lipase raises the triglyceride content in ApoB-containing lipoproteins, increasing vulnerability to oxidation.¹⁸⁰ HDL maturation is defective, intensifying inflammatory and oxidative stress and possibly further impairing reverse cholesterol transport. Dyslipidemia associated with end-stage renal disease is clinically resistant to traditional agents.^{185–187} Holzer et al¹⁷² found that the changes in HDL proteomic composition in hemodialysis patients correlated with significantly reduced macrophage cholesterol efflux mediated by both scavenger receptor class B type 1 and ATP-binding cassette transporter A-1. Serum amyloid A1, albumin, and ApoC-III replaced the HDL apolipoproteins, ApoA-I and ApoA-II, contributing to HDL dysfunction. Lipoprotein-associated phospholipase A2, a risk factor for atherosclerosis^{188–192} and a participant in its initiation and progression,^{193,194} is normally carried by LDL, where it hydrolyzes oxidized phospholipids, producing inflammatory signaling molecules, chiefly nonesterified fatty acids, such as arachidonic acid, lysophospholipids, and various oxidized lipids. In uremic HDL, the lipoprotein-associated phospholipase A2 content was 2.8-fold higher, accompanied by phospholipid depletion in HDL molecules, further impairing the ability of HDL to receive cholesterol for removal.¹⁷² Yamamoto et al¹⁹⁵ reported that HDL from patients on chronic hemodialysis had a profoundly impaired ability to accept cholesterol from macrophages, less antichemotactic ability, and was unable to reverse elevated expression of macrophage cytokines (tumor necrosis factor- α , interleukin-6, interleukin-1 β) compared with HDL from matched controls without renal disease. HDL from patients with end-stage renal disease and taking statins showed no improvement in cholesterol efflux, but anti-inflammatory properties did improve. Remarkably, upregulation of ATP-binding cassette transporter A-1 and ATP-binding cassette transporter G-1 by liver X receptor activation increased the efflux to both control HDL and to the dysfunctional HDL from patients with end-stage renal disease. Comparison of HDL from patients with end-stage renal disease with and without diabetes and other comorbidities revealed that uremia was the most important determinant of HDL dysfunction. These data suggest that: targeting hypoactive cellular transporters may attenuate the depressed cholesterol efflux associated with uremia; interaction of HDL with macrophage cholesterol transporters may be normalized to suppress monocyte chemoattractant protein-induced chemotaxis; there may be distinct metabolic

pathways responsible for different HDL functions; and as a result, restoration of macrophage cholesterol efflux and the diminished anti-inflammatory properties of dysfunctional HDL may be required to improve residual risk.

The functional heterogeneity of HDL limits the information obtainable from conventional HDL cholesterol measurements, because an unknown amount of impaired HDL may impede or actually accelerate atherogenesis. High HDL cholesterol concentrations may not reflect the ability to efflux more cholesterol or protect the vascular wall, nor are lower HDL cholesterol levels always sensitive to HDL dysfunction. The complex properties of HDL are apparent in preclinical and clinical investigations. For instance, HDL cholesterol from normolipidemic patients with angiographically documented coronary heart disease may still raise monocyte chemotactic activity and the formation of oxidized LDL, and statins may improve one variable but still leave proinflammatory HDL.¹⁵⁴ Hence, raising total HDL cholesterol without a reliable clinical method of assessing HDL function, or identifying proatherogenic components, may prevent meaningful interpretation of results.

Rare hereditary deficiencies in lecithin cholesterol acyltransferase impair the ability to esterify free cholesterol and interfere with reverse cholesterol transport, and would be expected to increase the risk of atherosclerosis. However, such associations are inconsistent and conflicting.¹⁹⁶ The paradox of severe, long-standing HDL deficiency in the absence of atherosclerosis in these patients may be due to the small numbers of individuals in studies, but a satisfactory explanation casts some doubt on the “HDL hypothesis”. An additional challenge to the HDL hypothesis was provided by Voight et al,¹⁹⁷ who conducted a Mendelian randomization analysis to explore the relationship between HDL cholesterol and the incidence of myocardial infarction. They used a rare variant of the endothelial lipase gene (*LIPG* Asn396Ser, minor allele frequency about 2.6%), which was associated with elevated HDL cholesterol (0.14 mmol/L, 6 mg/dL, or higher), but not with changes in LDL cholesterol or triglycerides. Subjects with the variant were exposed to lifelong high concentrations of HDL cholesterol because of their genotype. Based upon the higher HDL cholesterol values observed, one would have expected about 13% fewer myocardial infarctions, but this was not the case, implying that HDL cholesterol is not causally related to cardiovascular events. In contrast, gene variations that raised LDL cholesterol also raised cardiovascular risk, and vice versa; estimates from epidemiological studies were concordant with those from genetic analysis.

A genetic score composed of 14 variants affecting HDL cholesterol was also found to be unrelated to the risk for myocardial infarction.¹⁹⁷ These data support the belief that simply raising total HDL cholesterol may not be cardioprotective, and that HDL quality may be a better therapeutic target than HDL quantity. The inverse association of HDL cholesterol with MCVE would then be explained by HDL tracking with other independent variables, such as excessive visceral fat, inadequate physical activity, tobacco use, insulin resistance, a prothrombotic phenotype and/or high levels of triglyceride-rich remnant lipoproteins, small dense LDL, or C-reactive protein levels.

Overall, two concepts emerge that contradict past assumptions and will affect future practice. First, the small contribution of tissue cholesterol efflux to the plasma HDL cholesterol pool and the functional heterogeneity of HDL particles dispel the belief that HDL cholesterol values reflect reverse cholesterol transport at the level of macrophage cholesterol efflux. Second, circulating HDL cholesterol levels may not be a valid index of cardiovascular protection.

Caveats notwithstanding, infusing healthy HDL, certain methods of raising ApoA-I, use of ApoA-I mimetics or reconstituted or delipidated HDL may reverse some deterioration in HDL function, raise pre- β -HDL levels, and have the potential to increase reverse cholesterol transport robustly and slow atherogenesis.^{154,198} As a result, a number of HDL-based therapies to either stimulate ApoA-I production or the number of functional HDL particles are being investigated. Preclinical evidence for efficacy has been provided by raising ApoA-I production transgenically or using viral vectors, after which decreases in plaque macrophage and lipid content, increases in collagen, and lesion regression have been observed.¹⁹⁹ Induction of ApoA-I appears to be a viable strategy for cardiovascular protection, stimulating synthesis by raising the amount of ATP-binding cassette transporter A-1 in the liver, thereby promoting HDL assembly,²⁰⁰ or in patients by inducing the *ApoA-I* gene, although preliminary results using at least one oral drug, RVX-208, have been disappointing.²⁰¹ Similarly, introduction of ApoA-I or genetic variants,²⁰² infusion of reconstituted HDL,²⁰³ or reinfusion of selectively delipidated HDL²⁰⁴ are additional techniques that use the same principle. Remarkably, both ApoA-I Milano and delipidated HDL may cause lesion regression within months, as compared with the years required when intensive statin therapy is used.

Metabolic syndrome, diabetes, vascular disease, and residual risk

As the prevalence of overweight, obesity, diabetes, and hypertension rises in the population, elevated markers of

glucose intolerance, endothelial dysfunction, and inflammation may be found in a larger proportion of primary care patients not yet diagnosed with traditional risk factors or cardiovascular disease. This is particularly true of diabetes, a disease with beginnings as early as 20 years before a formal diagnosis.^{205–208} Current evidence indicates that there is a continuum of risk in such patients that extends through the point of actual diagnosis and possibly for decades thereafter. The deleterious effects of insulin resistance not only produce generalized changes in cellular metabolism, but also tissue-specific alterations leading to considerable pathology. These changes extend well beyond the lipidome, increased macrovascular and microvascular complications, and residual risk. Among the many examples are sympathetic overactivity and hypertension due to hyperinsulinemia, and, in the heart, regressive changes in myosin, restricted substrate availability and utilization, adverse effects upon cardiomyocyte function, oxidative metabolism, and genetic expression.²⁰⁹

As mentioned, all components of the atherogenic triad, ie, low HDL cholesterol, increased triglyceride levels, and elevated small dense LDL cholesterol, characteristic of patients with diabetes and metabolic syndrome, add additional cardiovascular risk. While elevated LDL cholesterol is not typical of these two syndromes, statin therapy remains the evidence-based initial target for such patients, although the first two features of atherogenic dyslipidemia may not be significantly improved by statin drugs. Patients with diabetes have a greater number of MCVE, worse clinical outcomes after events, and poorer risk profiles than their counterparts without the disease. MESA (the Multi-Ethnic Study of Atherosclerosis) compared the incidence of coronary artery calcium in 2,927 individuals without coronary artery calcium at baseline and progression of coronary artery calcium in 2,735 subjects with coronary artery calcium at baseline, divided according to the presence of: neither metabolic syndrome nor type 2 diabetes, metabolic syndrome without type 2 diabetes, type 2 diabetes without metabolic syndrome, and both type 2 diabetes and metabolic syndrome.²¹⁰ In a second calcium scan done after a mean of 2.4 years, as expected, there was greater progression in these four groups, advancing as the burden of glucose intolerance and risk increased, being lowest in patients with metabolic syndrome without type 2 diabetes and highest in those with both type 2 diabetes and metabolic syndrome. About 30% of patients with diabetes had progression, which was greatest in those with coronary heart disease. After an additional follow-up period of 4.9 years, coronary artery calcium progression was able to predict coronary heart disease events in patients with metabolic

syndrome and without type 2 diabetes, as well as in those with type 2 diabetes.

While oxidative stress and mitochondrial dysfunction are regarded as fundamental sources of molecular pathology in diabetes,²¹¹ metabolic connections between inflamed adipose tissue and cardiometabolic risk have also recently received particular attention.^{212–214} Central mechanisms connecting insulin resistance, lipoprotein changes, and cardiovascular risk include excess release of free fatty acids from adipose tissue, converted in the liver to triglycerides, leading to the combined defects of hepatic oversecretion of triglyceride-rich VLDL and impaired clearance of these particles, in association with higher plasma levels of ApoC-III.²¹⁵ The lower activity of lipoprotein lipase associated with insulin resistance contributes to elevations in triglycerides and VLDL. Exchange of cholesteryl ester in LDL cholesterol and triglycerides in VLDL via CETP and subsequent hydrolysis of triglyceride-rich LDL by lipoprotein lipase or hepatic lipase increases the number of small dense LDL particles with a diameter <25.5 nm. Small dense LDL is particularly atherogenic, in part because of lower affinity for the hepatic LDL receptor, prolonged plasma half-life, size, number, increased surface exposure of proteoglycans-binding residues in the ApoB-100 they contain, a raised ApoC-III content with greater affinity for arterial versican and biglycan, and depletion of protective lipophilic antioxidants (such as ubiquinol and vitamin E) rendering small dense LDL more susceptible to oxidative and proteolytic modification, facilitating macrophage uptake and foam cell formation. These particles are prominent in the atherogenic triad, correlating directly with serum triglyceride levels and inversely with the value of HDL cholesterol in the metabolic syndrome.²¹⁶

Clinically, excessive free fatty acid concentrations correlate with creatine kinase MB and oxidized LDL levels post myocardial infarction, as well as the severity and complications of myocardial infarction, including heart failure.²¹⁷ An ischemia-associated shift in myocyte substrate utilization from aerobic metabolism of free fatty acids to anaerobic glycolysis and the unwanted consequences have been known for some time.^{218,219} Among these are the promotion of oxidative stress and atherogenesis. High free fatty acid concentrations not only reflect myocardial injury, but likely participate in the development of insulin resistance.

Although glycation is a factor in pathogenesis and glycated small dense LDL are prone to oxidation, the role of advanced glycation end products and their receptors in type 2 diabetes-associated reverse cholesterol transport impairment remains uncertain.^{220,221}

A hypothesis that unites some features of diabetes, ie, insulin resistance, oxidative stress, elevated saturated fatty acids, endoplasmic reticulum stress, macrophage apoptosis, and defective resolution of inflammation with atherosclerotic plaque progression has been proposed by Tabas et al.^{63,222} In this model, persisting inflammation, defective efferocytosis, and egress of inflammatory cells leads to necrosis and an increase in plaque volume.

Overall, the components of metabolic risk are associated with atherogenic progression, MCVE, and increased mortality.^{223,224}

In 69 statin-treated male patients with coronary heart disease and LDL cholesterol at target levels <70 mg/dL, the relationship between low HDL cholesterol (<40 mg/dL), high triglycerides (>150 mg/dL) and dysfunctional HDL, with plasma adiponectin and insulin levels were studied.²²⁵ After adjustment for age and waist circumference, those with low HDL cholesterol and high triglycerides had higher fasting insulin and homeostatic model assessment values, lower adiponectin concentrations, and reduced cholesterol efflux than those with normal lipid levels. Low levels of adiponectin and ApoA-I accounted for 10.7% and 3.9% for the low cholesterol efflux, respectively. Although this study was small, the patients were typical of those commonly seen for re-evaluation and procedures, in whom residual risk takes its greatest toll. Adiponectin appears to be intimately involved not only in the fundamental pathogenesis of insulin resistance, but also in the biology of HDL and inflammation.^{226–229} Hypertriglyceridemic phenotypes manifest low plasma adiponectin concentrations, which correlates with increased ApoA-I catabolism.

Clinically, the ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease), and VADT (Veterans Affairs Diabetes Trial) studies found no significant improvement in cardiovascular endpoints with intensive glucose control, and ACCORD found no benefit from intensive antihypertensive or fibrate add-on therapy to statins, although subgroups provided further information.²³⁰ Simultaneous optimal management of coexisting risk factors, ie, hyperglycemia, hypertension, and dyslipidemia, is perhaps more effective in lowering cardiovascular risk in diabetic patients than intensive glucose control.^{230–232}

How does vascular disease develop in insulin-resistant patients likely to have high residual risk?

Mechanisms linking hyperglycemia with vascular dysfunction and microvascular complications of type 2 diabetes involve several classical pathways.

Protein glycation: effects of AGEs and their receptors

Advanced glycation end products (AGEs) are pro-oxidant derivatives of sugars nonenzymatically and covalently bonded with the amino groups of proteins, aminolipids, and nucleic acids that accumulate during aging and age-related diseases.²²⁰ Driven by oxidative stress, these compounds irreversibly rearrange over time, depositing within endothelial walls and other structures. Cells that are unable to lower inward glucose transport in the face of hyperglycemia, such as endothelial and mesangial cells, are most vulnerable. In these cells, nicotinamide adenine dinucleotide (NADH) levels may rise and increase the mitochondrial proton gradient sufficiently to interfere with the electron transport chain. Persisting adverse effects of antecedent hyperglycemia, consisting of progression of disease and development of complications, even though the hyperglycemia has been corrected, is called “metabolic memory.” This long-term responsiveness to early poor metabolic control upon later clinical outcomes, and development or progression of hyperglycemia-related microvascular disease during a subsequent period of euglycemia, may partly be mediated by AGEs, in addition to oxidative stress, inflammation, and epigenetic factors.^{233–236} Tissue damage by AGEs occurs through cross-linking and altered protein function, especially for collagen, and by inducing apoptotic cell death. Extracellular matrix components become unable to interact with each other and with receptors. Guanidines, including metformin, may prevent AGE reactions. The receptor for AGE (RAGE), a signal transducer, mediates the actions of a common antigenic AGE ligand in diabetics, ie, (carboxymethyl)lysine-protein adducts, although other receptors exist which lead to prolonged cellular perturbations. Binding of plasma protein-derived AGE with receptors activates endothelial cells, vascular smooth muscle cells, monocytes, and T cells, increases expression of proinflammatory cytokines, increases production of reactive oxygen species, and activates the transcription factor, NF- κ B. Damage may be widespread, not only in the vascular system but also in the kidney, retina, and nerves, and includes altered permeability, decreased nitric oxide production, promotion of a prothrombotic state, and pathologic shear stresses.²³⁷ Toxic RAGE plays an important role in the pathogenesis of vasculopathy in diabetics,²³⁸ and inhibition of AGE formation and its interactions is considered a potential therapeutic target.^{239,240}

Extensions of the metabolic memory hypothesis also postulate that after sustained exposure to reactive oxygen and nitrogen species, multiple permanent changes in proteins,

nucleic acids, etc eventually produce irreversible molecular pathology and microvascular disease, reaching a “point of no return.” These lead to upstream endothelial dysfunction and macrovascular pathology.

Interestingly, it is currently believed that significant accumulation of AGEs precedes the development of diabetes, and that food sources of AGE contribute to oxidative stress and insulin resistance by depletion of antioxidant defenses AGE receptor-1 and sirtuin 1. Restriction of high amounts of AGE-laden, thermally-processed foods, which increase appetite, promote overnutrition, and further metabolic disease, is a viable therapeutic approach.

Lipoprotein glycation

Glycation of lipoproteins is a modification which alters their properties, kinetics, and function. Glycation of LDL and HDL accelerates atherogenesis, ie, glycated LDL decreases nitric oxide production, activates endothelial cells, raises expression of adhesion molecules, and promotes platelet aggregation. In addition, lipoprotein glycation results in net enrichment of ApoB-containing lipoproteins due to greater transfer of cholesteryl ester by CETP. HDL glycation also significantly slows the rate of cholesterol esterification by lecithin cholesterol acyltransferase.

Glycated LDL is more susceptible to oxidation, so that hyperglycemia increases both glycated LDL cholesterol and oxidized LDL cholesterol.^{241–244} AGEs also increase the production of oxidized LDL by macrophages. Even short-term hyperglycemia results in substantial glycation of LDL cholesterol. Because of an LDL half-life of approximately 3 days, there is rapid formation of new nonglycated protein, and LDL glycation reflects variations in blood glucose over a shorter period than does glycosylated hemoglobin (HbA_{1c}). Hyperglycemia not only delays LDL clearance, but affinity of glycated LDL for arterial proteoglycan rises. Both glycated LDL and oxidized LDL enhance uptake of LDL cholesterol by macrophages and slow uptake of LDL cholesterol by the hepatic LDL receptor. Because the affinity of glycated LDL for scavenger receptors on macrophages remains unchanged, but the affinity for the hepatic LDL receptor decreases, the proportion of LDL cholesterol taken up by hepatocytes falls.²⁴⁵

In individuals with and without diabetes, concentrations of circulating glycated LDL cholesterol are usually higher than those of oxidized LDL, and the same is true for small dense LDL, although small dense LDL is more susceptible to glycation, even in nondiabetic persons. In patients with-

out diabetes, with metabolic syndrome, and with diabetes, small dense LDL is preferentially glycated, as compared with LDL. Interestingly, in diabetics, since glycated small dense LDL predominates heavily among glycated ApoB-containing lipoproteins, the amount of glycated ApoB in the plasma correlates not with HbA_{1c}, but with the amount of small dense LDL.²⁴¹ Both hyperglycemia and elevations in LDL cholesterol raise the extent of glycation and small dense LDL cholesterol. Statins effectively lower small dense LDL cholesterol levels, leading to a lower glycated LDL burden in diabetics. Hence, control of small dense LDL cholesterol using statins and other agents in patients with type 2 diabetes and metabolic syndrome may be more important than control of glycemia in reducing future cardiovascular risk. As mentioned above, while HDL is more resistant to oxidation and glycation than LDL, glycation of HDL impairs the latter's antiatherogenic capabilities, in part because loss of antioxidant potency renders it unable to protect LDL from proatherogenic modifications, but also because it reduces the anti-inflammatory and antiapoptotic capabilities of HDL.

Glucose metabolism through the polyol pathway

In patients with hyperglycemia, excess glucose is reduced to sorbitol by aldose reductase. This reaction consumes NADPH, the reduced form of nicotinamide adenine dinucleotide phosphate (NADP⁺). Because NADPH is also needed to regenerate reduced glutathione, the aforementioned reaction induces oxidative stress.^{246,247} In a second step, sorbitol is oxidized to fructose by sorbitol dehydrogenase, and NAD⁺ is reduced to NADH. Insufficient production of nitric oxide, which is common in diabetics, may promote glucose flux through the polyol pathway. At normal levels of glucose (5 mmol/L), about 3% of glucose is metabolized via aldose reductase, and at high levels (20 mmol/L), over 30% of glucose can be reduced by aldose reductase. Sorbitol does not cross membranes, and may raise osmotic pressure in cells when polyol pathway activity is high. Higher polyol pathway flux correlates with lower intracellular concentrations of nitric oxide and glutathione. Animal studies indicate that overexpression of the *aldose reductase* gene accelerates some type 2 diabetes complications. The antioxidant and signaling functions of aldose reductase are linked, so that attempts to inhibit aldose reductase may also affect protein kinase C (PKC) activity and activation of NF- κ B protein. Finally, high aldose reductase activity may contribute to

AGE formation, increase PKC expression, and diacylglycerol synthesis by raising oxidative and osmotic stress (see next page). Inhibition of aldose reductase has already been used in clinical trials for diabetic complications and other inflammatory disorders.

Activation of PKC and p38 mitogen-activated protein kinases

Hyperglycemia raises levels of dihydroxyacetone phosphate, the glycolytic intermediate, which is reduced to glycerol-3-phosphate, increasing the synthesis of diacylglycerol, in turn leading to chronic activation of a family of PKC enzymes (serine/threonine-related protein kinases) that regulate cellular functions and affect many signal transduction pathways. These include vascular permeability, contractility, extracellular matrix synthesis/turnover, hormone receptor proliferation/turnover, endothelial nitric oxide synthase expression, cell growth, apoptosis, angiogenesis, cytokine activation in macrophages, leukocyte adhesion, and changes in enzymatic activities of mitogen-activated protein kinase, cytosolic phospholipase A2, Na⁺-K⁺-ATPase, and PI3 kinase.²⁴⁸ All these functions are abnormal in diabetes, promoting vascular complications, such as diabetic cardiomyopathy, and correlate with overactivity of diacylglycerol production.²⁴⁹ In obese nondiabetic humans, diacylglycerol content of hepatic lipid droplets accurately predicts insulin resistance.²⁵¹ The PKC pathway and α , β 1/2, and δ isoform activation in the retina, aorta, heart, and renal glomeruli are associated with vascular pathology in those tissues, as well as in macrophages. PKC-dependent activation of NAD(P)H oxidase increases oxidative stress, which plays a key role in mediating responses to hyperglycemia. In smooth muscle, orchestrated activation of particular PKC isoforms, mitogen-activated protein kinases, nuclear transcription factors, the Janus family of activated kinases, and signal transducers and activators of transcription increase growth, proliferation, migration, and hypertrophy.²⁵² Recently, hyperglycemic activation of PKC- β and the resulting endothelial dysfunction was linked to release of the protease, calpain, and upregulation of interactions involving endothelial intercellular adhesion molecule 1 and leukocyte-endothelium.²⁵³ Ruboxistaurin mesylate, a selective inhibitor of the PKC- β isoform, blocks some deleterious consequences of PKC activation and reverses endothelial dysfunction, preserves renal glomerular filtration rate, and prevents visual loss in diabetic patients. Inhibitors of the PKC isoforms favorably influence the microvascular complications of type 2 diabetes.^{251–256}

Increased activity of the pentose phosphate pathway

Normally glucose is metabolized during glycolysis by conversion to fructose-6-phosphate and then by the remainder of the pentose phosphate pathway (also called the hexose monophosphate shunt). Hyperglycemia shunts some fructose-6-phosphate (through the enzyme glutamine:fructose 6-phosphate amidotransferase) to glucosamine-6-phosphate, which then glycosylates serine and threonine residues on transcription factors. These modifications interfere with gene expression and increase secretion of plasminogen activator inhibitor-1, matrix metalloproteinases, and transforming growth factor- β 1. Other nuclear and cytoplasmic proteins, including endothelial nitric oxide synthase, undergo similar changes, all potentially contributing to vascular damage.

Mitochondrial dysfunction, oxidative stress, insulin resistance, and roles of hyperglycemia and excess fatty acids

Oxidative stress is a central feature in the pathogenesis of diabetes, metabolic syndrome, and atherosclerosis.^{211,257–260} A common mechanism by which hyperglycemia accelerates vessel damage mentioned in this discussion is mitochondrial overproduction of superoxide in vascular endothelium. Not only does superoxide activate pathways through the mechanisms discussed above, but adds more molecular pathology, including direct suppression of endothelial nitric oxide and prostacyclin production, defective angiogenesis during ischemia, stimulation of other proinflammatory pathways, and induction of persisting epigenetic changes that maintain inflammation beyond periods of glycemia, contributing to metabolic (hyperglycemic) memory.²⁶⁰

Basically, in response to hyperglycemia and higher concentrations of the electron donors NADH and FADH₂ generated by increased metabolism of substrate in the tricarboxylic acid cycle, greater activity of the electron transport chain pumps more protons across the inner mitochondrial membrane. When the membrane potential rises to a threshold, electron transport is inhibited at complex III, electrons pass through coenzyme Q and reduce O₂ to superoxide. Excess energy not used for ATP production in mitochondria at complex IV is dissipated as heat through uncoupling proteins. In this model, superoxide production is driven by the metabolic load of hyperglycemia. Similarly, high levels of free fatty acid oxidation increase oxidative stress, stimulate AGE, and activate PKC, the hexosamine pathway, and

NF- κ B to the same degree as hyperglycemia. Increased free fatty acid flux from insulin-resistant visceral adipocytes to vascular endothelium may link insulin resistance and vascular disease. Superoxide reacts with nitric oxide to form peroxynitrite, a pernicious free radical which brings about enzymatic uncoupling of endothelial nitric oxide synthase, leading to more superoxide production. Mitochondrial contribution to oxidative stress during glycemia therefore arises from superoxide formation and its free radical progeny, proinflammatory enzymes, and uncoupled endothelial nitric oxide synthase. Peroxynitrite (ONOO⁻) may also damage mitochondrial DNA, resulting in a dose-dependent decrease in mitochondrial DNA-encoded mRNA transcripts. Mitochondrial protein synthesis is likewise inhibited by ONOO⁻, leading to lower cellular ATP levels and defective mitochondrial redox function.²⁶¹

Reactive oxygen species also deplete the availability of arginine, and oxidize the endothelial nitric oxide synthase cofactor tetrahydrobiopterin (BH₄) to dihydrobiopterin (BH₂), both of which contribute to glycemia-associated endothelial dysfunction.²⁶² Nitric oxide synthesis is further suppressed by competitive inhibition of endothelial nitric oxide synthase via asymmetric dimethylarginine, given that oxidative stress promotes synthesis of asymmetric dimethylarginine and inhibits its catabolism, potentially leading to endothelial impairment. Clinically, high levels of asymmetric dimethylarginine are found in patients with hypertension, CHD, dyslipidemia, diabetes and chronic renal disease; high concentrations strongly and independently predict MCVE, cardiovascular-related, and all-cause mortality.

Mitochondrial dysfunction and intracellular free fatty acids or their metabolites also play a role in both the insulin resistance and β cell failure characteristic of type 2 diabetes. First, overexpressed cytokines released by adipocytes may lower the responsiveness of skeletal muscle and liver to insulin. Second, fatty acid-mediated inhibition of insulin signaling occurs through a serine kinase cascade, leading to inactivation of insulin receptor substrate-1.²⁶³ Downregulation of this substance interrupts signal transmission from insulin and insulin-like growth factor-1 receptors to intracellular pathways (PI3 kinase/Akt and Erk mitogen activated protein (MAP) kinase). In skeletal muscle and adipose tissue, translocation of intracellular vesicles containing the glucose transporter isoform 4 to the plasma membrane is prevented, creating the insulin resistant phenotype.^{264,265} Third, increased mitochondrial production of superoxide may raise uncoupling protein-2 activity and lower glucose-stimulated insulin secretion in the β cell.²⁶⁶

The molecular details of impaired insulin release, signaling, and resistance are complex, remain uncertain, and several pathways have been proposed,²⁰⁹ while new data continue to open additional possibilities. Involvement of mitochondrial biogenesis, DNA damage, microRNAs, and endoplasmic reticulum stress are discussed elsewhere.^{63,224,267–273} Areas of recent interest include the influence of intestinal microbiota on lipopolysaccharide entry and TLR-4 activation to increase cardiometabolic risk,^{274–276} and hyperglycemia-related overexpression of the sodium-glucose cotransporter 2 in the proximal tubule to increase renal reabsorption of glucose.²⁷⁷ How multiple, tissue-specific insulin signaling pathways that have been described, intersect to raise cardiovascular risk, is of interest in creating a unified panorama of events. For instance, nutrient excess and obesity is associated with insulin resistance and, ultimately, inflammation through NF- κ B activation. Elevated levels of free fatty acids lead to insulin resistance in muscle and liver through the pathways presented previously. Considerable evidence now indicates that free fatty acids, such as palmitate, activate TLR-4, which then mediate the inflammatory response.^{278,279} The TLR-4 pathway accelerates hyperlipidemia-induced atherogenesis in animal models through release of proinflammatory cytokines, recruitment and activation of immune cells, and promotion of foam cell formation.²⁸⁰ As such, the innate immune system appears to be involved in endothelial inflammation and impaired nitric oxide production in vascular disease associated with free fatty acid excess in obesity. The gene *Bcl10* is a component of a signaling complex, the signalosome, which modulates lymphocyte proliferation and B and T cell antigen receptor signaling leading to NF- κ B activation. *Bcl10*-deficient mice are protected against hepatic NF- κ B activation as well as from free fatty acid-induced insulin resistance.²⁸¹ For this reason, interfering with *Bcl10* signaling may be a possible therapeutic target in preventing the inflammation and insulin resistance induced by dietary fats.²⁸²

Further delineation of mediators and pathways of insulin resistance and mitochondrial dysfunction may uncover more therapeutic targets to attenuate the metabolic effect of risk factors or slow atherosclerosis. Insulin signaling supports the integrity of the mitochondrial electron transport chain by suppressing isoforms of the class O forkhead box transcription factors (FoxO) in endothelial cells by stabilizing the NAD⁺/NADH ratio.²⁶³ FoxO also participates in several atherogenic pathways in endothelial cells, and suppression of these transcription factors may be beneficial in reducing the vascular complications associated with diabetes.²⁸³ Murine data suggest

the potential to reduce atherosclerosis by up to 77% through FoxO inhibition under appropriate circumstances.²⁸³

Plasma triglyceride levels and residual risk

Support for the view that triglyceride concentrations are independent risk factors has waxed and waned over the past three decades, and the debate continues.^{210,284–288} Clinical evidence that elevated triglyceride levels raise risk independently of LDL cholesterol concentrations has been available for some time,²⁸⁵ yet after adjustment for covariates, the strength of the triglyceride and risk association falls or disappears.²⁸⁹ Plasma triglyceride levels in Americans have increased during this period, paralleling the dual epidemics of obesity and type 2 diabetes. Epidemiologic, clinical, and genetic data indicate that triglyceride values do predict coronary heart disease and stroke, but are not primary offenders in creating risk. Rather, it is believed that the cholesterol in triglyceride-rich lipoproteins, released by the liver or intestine, is responsible for the additional cardiovascular risk.^{289–291} In the fasting individual, triglyceride-rich lipoproteins are chiefly composed of VLDL and intermediate density lipoproteins, whereas postprandially, triglyceride-rich lipoproteins also include additional chylomicron remnants. In insulin-resistant and other syndromes characterized by fasting and postprandial elevations in triglyceride levels, the triglyceride/cholesterol content of lipoproteins changes accordingly. The triglyceride level may then serve as a marker for both triglyceride-rich lipoproteins and ApoC-III.²⁹¹ In patients with triglyceride levels greater than 400 mg/dL, the amount of cholesterol carried by triglyceride-rich lipoproteins may exceed that in LDL cholesterol or HDL cholesterol.²⁸⁸ Since atherogenic remnants of triglyceride-rich lipoproteins are not captured by LDL cholesterol or HDL cholesterol in the standard lipid profile, they can be a significant source of residual risk in patients with obesity, diabetes, metabolic syndrome, and chronic renal disease.²⁸⁹

A recent report regarding ATP-binding cassette transporter G-1 activity, lipoprotein lipase, and foam cell formation in the presence of high levels of triglyceride-rich lipoprotein is of interest.¹⁶² Although ATP-binding cassette transporter G-1 is classically believed to protect against macrophage foam cell formation, in humans, rather than in mice used in prior studies, ATP-binding cassette transporter G-1 activity does not contribute as heavily to macrophage foam cell cholesterol efflux.^{292,293} In addition to the lipolytic activity of lipoprotein lipase within vessels, lipoprotein lipase may have other functions intracellularly. In human

macrophages derived from monocyte cultures, a fall in ATP-binding cassette transporter G-1 expression leads to lipoprotein lipase concentration within cholesterol-rich domains in cell surfaces, thereby reducing bioavailability and activity of lipoprotein lipase.¹⁶² Consequently, when triglyceride levels are high, lipoprotein lipase-mediated accumulation of lipids in foam cells are diminished when ATP-binding cassette transporter G-1 expression falls, suggesting a potentially unfavorable role for ATP-binding cassette transporter G-1 in this particular setting.

Hepatic oversecretion and/or slowed degradation of triglyceride-rich lipoprotein are frequently encountered in diabetes and the metabolic syndrome. Raised production of ApoC-III in the liver may decrease catabolism of triglyceride-rich lipoproteins. Accumulation of free fatty acids and triglycerides leads to fat deposition in the liver, and VLDL is overproduced. Hypertriglyceridemia is also associated with activation of NF- κ B and inflammation, oxidative stress, smooth muscle cell pathology, and impaired endothelial function and repair.²⁸⁵ Importantly, hydrolysis of triglyceride-rich lipoprotein by lipoprotein lipase leads to proinflammatory rises in nonesterified fatty acids and cholesterol-rich remnant-like particles. Remnant-like particles are commonly elevated in obese patients with insulin resistance,²⁹⁴ type 2 diabetes with the atherogenic triad,²⁹⁵ metabolic syndrome,²⁹⁶ and familial combined hyperlipidemia,²⁹⁷ all of which are associated with a higher risk for atherosclerosis.^{297–299} Elevations in cholesterol-rich remnant-like particles are associated with impaired rheology,³⁰⁰ upregulation in endothelial adhesion molecules (intercellular adhesion molecule 1, vascular cell adhesion molecule 1), and proinflammatory cytokines such as interleukin-1 β , oxidative stress, and endothelial dysfunction.²⁹⁵ Cholesterol concentrations in remnant-like particles are 5–20 times the typical amounts in LDL, easily cross the endothelium, and are readily taken up by scavenger receptors on macrophages, contributing to foam cell formation and plaque volume.³⁰¹ Triglyceride-rich lipoproteins may also activate coagulation mechanisms and suppress fibrinolysis. Lastly, triglycerides and triglyceride-rich VLDL may be associated with albuminuria and development of diabetic neuropathy.

There is some controversy regarding conditions under which triglyceride-rich lipoproteins may initiate inflammatory changes in endothelium leading to atherosclerosis.⁴⁷ Available evidence suggests that increased lipoprotein content of ApoC-III may play a pivotal role, activating NF- κ B through a separate PKC pathway, leading to expression of adhesion molecules and recruitment of monocytes.⁴⁷

Recently, in a Mendelian randomization approach, using genetic variants closely associated with a single lipoprotein but without effects on other lipoproteins, Varbo et al³⁰² examined whether elevations in remnant cholesterol affected risk for coronary heart disease. Such genotypes experience lifelong exposure to their respective lipoprotein phenotypes, strengthening the probability of a causal effect on risk for coronary heart disease, as compared with observational trials, in which exposure is limited to a relatively brief study period. A total of 73,513 participants were genotyped, of whom 11,984 had coronary heart disease. Fifteen genetic variants were used, influencing: nonfasting remnant cholesterol alone; nonfasting remnant cholesterol and HDL cholesterol combined; HDL cholesterol alone; or LDL cholesterol alone as a positive control. The study found that a 1 mmol/L (39 mg/dL) rise in nonfasting remnant cholesterol was associated with a 2.8-fold causal risk for coronary heart disease, which was independent of lowered HDL cholesterol. Although confirmation is needed, these data clearly suggest that remnant cholesterol is a risk factor for coronary heart disease, and is included in the value of non-HDL cholesterol, discussed in the next section. The primary current target for dyslipidemia therapy, LDL cholesterol, does not reflect remnant cholesterol. A higher level of remnant-like particles contributes to residual risk, given that the effect of statins upon remnant cholesterol, although beneficial, may be variable in time course and/or incomplete.

Some studies, most notably the PROVE-IT TIMI 22 study,¹²⁷ showed that on-treatment triglyceride values over 150 mg/dL were independently associated with a higher risk of MCVE after acute coronary syndrome. However, the association is progressively lost as additional variables are added to the model, including HDL cholesterol, ApoB/ApoA-I, diabetes, glucose, hypertension, and smoking.³⁰³ Although atherogenic dyslipidemia is closely associated with cardiovascular risk, details of the relationships between triglycerides, HDL, biomarkers, initiation and progression of atherosclerosis, and clinical outcomes are complex, incompletely understood, and remain in flux. On the basis of epidemiologic evidence, mechanistic pathophysiologic studies, animal models, genetics, and human interventional data, the European Atherosclerosis Society concluded that both triglyceride-rich lipoproteins and low HDL cholesterol were involved in atherogenesis.²⁸⁹ In a scientific statement, the American Heart Association (AHA) also reviewed the appreciable data that elevations in triglyceride levels were undesirable, and defined the optimum fasting value of triglycerides <100 mg/dL as an index of metabolic health. Intensive lifestyle change was favored as the initial

approach for borderline or high levels, with the option of adding omega-3 fatty acids, reserving drugs for triglyceride levels >500 mg/dL.³⁰⁴ At about the same time, there was a separate re-evaluation of the use of fibrates in nondiabetics,³⁰⁵ and in diabetics without^{306,307} and with^{308,309} renal disease that is ongoing (see section on fibrates to follow). One author suggests that if the goal is to reduce triglyceride levels, then fibrates and omega-3 fatty acids might be options, but if the goal is modification of particle composition or to decrease ApoC-III-rich remnant lipoproteins, niacin might be chosen, keeping in mind the results of recent niacin trials.²⁸⁷ The balance between need for additional therapies to reduce high risk and caution imposed by lack of large-scale, well designed studies in hypertriglyceridemic patients is emphasized by Maki et al.³¹⁰

Non-HDL cholesterol and reduction of residual risk

Non-HDL cholesterol, obtained by subtracting HDL cholesterol from total cholesterol numerically, reflects the cholesterol concentration in intermediate density lipoprotein, VLDL, chylomicron and VLDL remnants, and lipoprotein(a), all atherogenic particles that may contribute to residual risk.

The upper normal cutoff for non-HDL cholesterol was set at 30 mg/dL above the LDL cholesterol cutoff, since the upper limit of optimal triglycerides is 150 mg/dL, corresponding to a calculated VLDL cholesterol of $150 \text{ mg/dL} / 5 = 30 \text{ mg/dL}$. After LDL cholesterol, the Adult Treatment Panel III recommended non-HDL cholesterol as a secondary target in patients with triglycerides ≥ 200 mg/dL. However, the changing phenotype of patients with cardiometabolic risk, with the ever-increasing prevalence of insulin resistance syndromes, has further diminished the value of LDL cholesterol as a primary target.

The value of measuring non-HDL as a broad index of atherogenic risk is well supported. Non-HDL was found to add predictive value and to correlate strongly with the atherosclerotic burden in the right coronary artery and upper aorta at autopsy.³¹¹ To determine the relationship between non-HDL cholesterol-lowering and coronary heart disease risk reduction for different lipid-modifying therapies, Robinson et al³¹² conducted a meta-analysis of trials using statins, fibrates, niacin, cholestyramine, diet, and ileal bypass. They found that for most lipid-modifying drugs used as monotherapy, there was a 1:1 relationship between non-HDL cholesterol reduction and coronary heart disease risk. The Strong Heart Study established that the predictive power of non-HDL

cholesterol persisted over a range of triglyceride values in diabetics.³¹³ In both primary and secondary prevention patients, non-HDL cholesterol predicted risk independently of triglyceride levels in the elderly as well.³¹⁴ In contrast, discordance between LDL cholesterol and LDL particles, non-HDL cholesterol, and ApoB becomes more significant as triglycerides increase beyond 150 mg/dL.

LDL cholesterol calculated using Friedewald's formula requires a fasting blood sample and introduces greater error as triglyceride levels rise. On the other hand, although some analytical issues remain when measuring HDL cholesterol clinically in hypertriglyceridemic patients, useful and stable non-HDL cholesterol values may be generated using a non-fasting sample, sometimes obviating the need for a direct LDL cholesterol assay. Masana et al³¹⁵ recently reported that discordance between LDL cholesterol and non-HDL cholesterol rose as triglycerides increased in patients with elevated triglycerides and LDL cholesterol within evidence-based targets. When triglycerides were >400 mg/dL and LDL cholesterol was on target, 86% had non-HDL cholesterol >130 mg/dL, and of the patients with triglycerides >400 mg/dL and a non-HDL cholesterol qualifying for further treatment, 40% had an LDL cholesterol value that was not actionable. Hence, when Friedewald's formula cannot be used because triglyceride levels exceed 400 mg/dL, 86% of patients with acceptable LDL cholesterol values require more therapy, and in those with moderate elevations in triglycerides (≥ 150 mg/dL), use of non-HDL cholesterol would double the number of patients eligible for further treatment. In other words, inattention to non-HDL cholesterol will potentially result in undertreatment of every other such diabetic patient for their dyslipidemia.

There is now a well developed literature reflecting the superior performance of non-HDL cholesterol compared with LDL cholesterol; non-HDL cholesterol is a strong predictor of all-cause and cardiovascular mortality, whereas LDL cholesterol is not. The Lipids Research Clinics Program Follow-up Study demonstrated the greater ability of non-HDL cholesterol to discriminate between levels of cardiovascular and all-cause mortality.³¹⁶ In the BARI (Bypass Angioplasty Revascularization Investigation) study, non-HDL cholesterol strongly predicted angina and non-fatal myocardial infarction.³¹⁷ The Women's Health Study documented that non-HDL cholesterol outperformed LDL cholesterol and ApoA-I, and was equivalent to measuring ApoB among healthy women.³¹⁸ Considerable evidence, however, indicates that ApoB predicts cardiovascular risk more accurately than does non-HDL cholesterol, although not sufficiently to overcome the practical

Table 1 Comparison of drugs and lifestyle measures that raise HDL cholesterol levels

Drug or lifestyle change	% HDL-C elevation
Niacin	15–35
Statins	5–10 (greatest for rosuvastatin at 6%–12%)
Fibrates	5–15
CETP inhibitors	25–138
Anacetrapib	Up to 138 (↓LDL-C about 40%, ↓Lp(a) about 36%)
Evacetrapib	Up to 129 (↓LDL-C about 36%)
Dalcetrapib	Development stopped
Torcetrapib	Development stopped
Bile acid sequestrants/ion exchange resins	5–10
Estrogens, oral	10–15
Lifestyle modifications	
Smoking	Smokers have 7%–20% lower HDL-C levels than nonsmokers
Weight	HDL-C↑ about 1 mg/dL for each 7 lb (3 kg) lost
Aerobic exercise	HDL-C↑ about 0.308 mg/dL per mile per week (0–30 m)
Alcohol	HDL-C↑ according to dose, 0–40 g of alcohol/day

Abbreviations: CETP, cholesteryl ester transfer protein; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

advantages of using non-HDL cholesterol.^{319–322} Other studies using carotid intima-media thickness and coronary artery calcium suggest that non-HDL cholesterol is also a better predictor of subclinical atherosclerosis than LDL cholesterol. Recent work shows that among patients treated with statins, the strength of associations of LDL cholesterol, non-HDL cholesterol, and ApoB with future MCVE is greatest for non-HDL cholesterol.³²³ In addition, non-HDL cholesterol is an independent predictor of cardiovascular disease in patients following myocardial infarction, with the largest effect of all lipid fractions,³²⁴ and an independent risk factor for stroke in healthy women. Finally, non-HDL cholesterol shows a close relationship with small dense LDL levels compared with other lipid parameters.

As mentioned previously, particularly in diabetic patients with an abundance of triglycerides, high levels of oxidative stress, and a proinflammatory phenotype, ApoB-containing atherogenic lipoproteins easily become modified, in part by uptake of cholesterol from HDL cholesterol, and form remnant lipoproteins. These remnants have physical characteristics favoring their accumulation within macrophages to promote atherogenesis. In addition, VLDL, oversecreted by the liver, and LDL may become enriched with ApoC-III, with

subsequent direct proinflammatory actions upon macrophages and endothelial cells. As noted by Masana et al and others, in patients with and without type 2 diabetes, non-HDL cholesterol levels are generally higher in the former, whereas LDL cholesterol values may be similar.^{315,325,326} Greater accuracy in monitoring and improving risk reduction in such patients will be assisted through the use of non-HDL cholesterol.

In summary, the ability of non-HDL cholesterol to better incorporate the total atherogenic lipoprotein burden, thereby reflecting residual risk, together with practical advantages compared with ApoB, makes non-HDL cholesterol an attractive marker for clinical use.^{1,318,327–330} Targeting non-HDL cholesterol, rather than LDL cholesterol, would prevent 300,000 more events over a 10-year period in the US adult population, although an ApoB strategy would improve the yield still further.³³⁰ Many observers believe that non-HDL cholesterol will be emphasized in Adult Treatment Panel IV. Since there is no additional cost when performing customary lipid profiles, non-HDL cholesterol should be included in all reports. This practice may also help to erode an educational inertial barrier in the understanding, interpretation, and wider application of non-HDL cholesterol in the future.

Can niacin lower residual risk? AIM-HIGH and HPS-2 THRIVE studies

Historically, niacin has been the most effective agent for raising HDL cholesterol, typically by 15%–35%, with slowed hepatic catabolism and/or increased production of ApoA-I, accompanied by lowering of triglyceride values by 15%–50% and favorable effects on ApoB containing lipoproteins (Table 1). In addition, niacin also raises HDL particle numbers, which may correlate better with antiatherosclerotic protection than HDL cholesterol under certain circumstances.^{331,332} Classically, it has been believed that niacin (a) slowed lipolysis of triglycerides in adipose tissue, lowering the availability of nonesterified fatty acids for triglyceride synthesis, and (b) inhibited hepatic diacylglycerol acyltransferase-2, now emphasized as the key contributor in reducing triglyceride synthesis and lowering liver fat content. Niacin also (c) promotes β oxidation of fatty acids in the liver and (d) raises post-translational hepatocellular ApoB degradation, with (b), (c), and (d) decreasing the secretion of VLDL and LDL. There has been some question about the ability of niacin to inhibit adipose lipolysis of triglycerides since work with mice deficient in the niacin receptor (GPR109A) do not show acute blocking of lipolysis, and agonists for GPR109A in humans lower free fatty acids acutely but do not produce typical lipid changes. During

long-term niacin therapy, there is also a substantial rebound of lipolysis, even as the triglyceride-lowering is maintained, leading to the suggestion that niacin-induced increases in oxidative type-1 muscle fiber content and associated greater utilization of fatty acids by skeletal muscle may contribute to the triglyceride lowering observed.^{333,334}

In addition, niacin promotes ATP-binding cassette transporter A-I activity leading to greater ApoA-I lipidation, increasing the amounts of stable lipid-poor ApoA-I/pre- β HDL, minimizing the renal clearance of lipid-free ApoA-I. The net effect is generation of more HDL cholesterol. Further, niacin decreases hepatocyte surface expression of b-chain ATP synthase, an HDL holoparticle receptor, lowering the endocytic uptake and catabolism of HDL ApoA-I without disturbing hepatocyte synthesis of ApoA-I, leaving a greater number of HDL ApoA-I particles in the circulation.³³⁵

A fall in secretion of triglyceride-rich VLDL lowers CETP activity, triglyceride transfer to acceptors VLDL and LDL, and increases HDL and LDL size. Niacin also lowers the LDL particle number by about 14%. Enhanced clearance of triglyceride-rich ApoB-100 is accentuated by statin administration.³³⁶ Niacin also has antioxidative and anti-inflammatory properties, inhibits cytokine-induced expression of chemokines and adhesion molecules, and improves endothelial function independently of lipid effects. Through activation of the GPR109A receptor (now called hydroxyl-carboxylic acid receptor) expressed in monocytes and macrophages, niacin lowers secretion of tumor necrosis factor- α and interleukin-6, and inhibits monocyte chemoattractant protein-induced recruitment of macrophages to slow atherosclerosis.³³⁷ Recently, a significant inverse relationship between cholesterol efflux capacity from macrophages and carotid intima-media thickness was demonstrated in healthy subjects, which was independent of HDL cholesterol levels.¹³³ In patients with coronary heart disease, raised efflux capacity was independently predictive of a decrease in risk of coronary artery disease, suggesting that HDL function, not HDL abundance, promotes macrophage cholesterol efflux, and correction of dysfunctional HDL might be the more suitable target to improve coronary heart disease outcomes. In this regard, Yvan-Charvet et al reported that treatment with niacin increases HDL cholesterol by about 30% and modestly improves the ability of HDL to induce macrophage cholesterol efflux, while suppressing inflammation in macrophages mediated by TLR-4.^{331,338}

Flushing is the major adverse effect, although liver toxicity, elevations in uric acid, and glucose intolerance are well-known.

The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial randomized 3,414 patients with coronary heart disease and atherogenic dyslipidemia to either extended-release niacin 1.0–2.0 g/day and simvastatin or to placebo and simvastatin.³³⁹ The dose of simvastatin was adjusted to an LDL cholesterol of 40–80 mg/dL, with ezetimibe 10 mg added if needed. It was designed with 85% power to demonstrate a 25% reduction in the primary MCVe endpoint. However, the group not receiving niacin increased their HDL cholesterol unexpectedly, the inter-group differences in HDL cholesterol were not sufficiently large (only about 4 mg/dL), and the trial was underpowered for the purpose intended. In addition, better control of low LDL cholesterol and drug titration was needed, and there was a 25% discontinuation rate in the niacin group. Nonetheless, the lack of improvement in those taking niacin was still considered a negative study, calling for premature early retirement for niacin. However, a systematic review of 11 niacin trials using meta-regression analysis found significant benefits of niacin on composite endpoints of any MCVe (odds ratio 0.66; 95% CI 0.49–0.89; $P = 0.007$) and major coronary heart disease events (odds ratio 0.75; 95% CI 0.59–0.96; $P = 0.02$) despite the inclusion of AIM-HIGH, but not HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events).³⁴⁰ There was no association between on-treatment HDL cholesterol levels and improvement in outcomes, leading the authors to consider a mechanism not reflected in total HDL cholesterol values. Among the possibilities are lipid effects not captured by conventional lipid profiles or the many extra-lipid actions of niacin. Examples include a reduction in lipoprotein(a), lipoprotein particle size distribution, and anti-inflammatory actions, such as lowering of C-reactive protein or lipoprotein-associated phospholipase A2, upregulation of adiponectin, or suppression of proinflammatory chemokines. Indeed, niacin-induced slowing and regression of atherosclerosis as well as plaque stabilization have been observed in animal models in the absence of significant changes in lipid profiles.^{137,341,342} The review concluded that defining the potential benefits of niacin solely by elevations in HDL cholesterol may be somewhat misdirected.

The HPS2-THRIVE trial³⁴³ enrolled 25,673 patients at high cardiovascular risk for cardiovascular events in the UK, Scandinavia, and the People's Republic of China. The study compared extended-release niacin 2 g and laropiprant, a prostaglandin D(2) receptor-1 antagonist to reduce flushing, with statin therapy (simvastatin 40 mg daily, or, if already

taking ezetimibe or a more potent statin dose, ezetimibe/simvastatin 10/40 mg), versus statin with or without ezetimibe. Patients in the study were to be followed for a median of 3.9 years using a primary composite endpoint of risk of coronary death, non-fatal myocardial infarction, stroke, or revascularization. Unfortunately, to the dismay of clinicians who hoped otherwise, the study not only failed to reach goals, but there were significant numbers of adverse effects, including an unexpectedly high incidence of myopathy.³⁴⁴ There were reductions in LDL cholesterol of 0.2586 mmol/L (10 mg/dL) and triglycerides of 0.373 mmol/L (33 mg/dL) among treated patients, but there was no statistically significant difference between MCVE in the niacin arm (event rate, 13.2%) and the placebo arm (event rate, 13.7%). There were approximately 30 adverse events/1,000 patients treated, and in those receiving niacin there was an increased absolute risk of 3.7% in diabetes complications, 1.8% of new-onset type 2 diabetes, 1.4% in infection, and 0.7% in bleeding, including hemorrhagic stroke. Merck announced that it would not pursue approval of the drug in the US.³⁴⁵ The European Medicines Agency began a review of preparations containing niacin, commenting that “the new data failed to show that the combination reduces the risk of major vascular events (such as heart attack and stroke), and a higher frequency of nonfatal but serious side effects was seen in patients taking the combination”.

About 10,000 of patients in the study were Chinese, a population known to have poor tolerance to both intensive statin therapy and niacin. The study design did not permit assessment of extended-release niacin alone. Without a placebo group, whether the results were due to ineffectiveness of extended-release niacin or confounding actions of laropiprant, with potentially complex but unexplored vascular effects, remain unknown. The involvement of ezetimibe, if any, was also unknown. There was no entry threshold of HDL cholesterol for the trial, leaving a study population with a spectrum of HDL cholesterol levels, presumably with a spectrum of possible responses. In addition, the baseline characteristics of patients enrolled, ie, an LDL cholesterol of 1.63 mmol/L (63 mg/dL) and an HDL cholesterol of 1.14 mmol/L (44 mg/dL), are not typical of those in whom niacin therapy is considered. Of patients treated, a rise of 6 mg/dL in HDL cholesterol values (about 14%) could have been inadequate to influence MCVE, using prior trials as a guide. Despite such methodologic flaws, the HPS2-THRIVE results cast more doubt about therapies to raise total HDL cholesterol concentrations for prevention of clinical events. Details were presented at the American College of Cardiology 2013 Scientific Sessions, preceding publication.^{343–346}

Although some data in older studies predate the widespread use of statin drugs, a number of researchers and clinicians continue to suspect a properly designed niacin study is still required before abandoning use of this agent. The HPS2-THRIVE data, while imperfect, strongly suggest that the side effects of niacin extended-release with laropiprant outweighed the benefits in the study population, which may not have been sufficiently representative to generalize. With waning enthusiasm among stakeholders, it is unlikely that further major efforts will be expended on this issue.

Can CETP inhibition reduce residual risk?

Despite the greater relationship between HDL function and vascular risk, an observed lack of protection afforded to patients by high HDL cholesterol in the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) study,³⁴⁷ and lingering doubt about whether the composition of larger, cholesterol-laden HDL that results after CETP inhibition functions normally, clinical interest in CETP inhibition has continued. As a result of electron microscopy data, a mechanism of action for CETP transfer of cholesteryl esters from atheroprotective HDL to atherogenic LDL has been proposed.²²¹ From studying single-particle image processing and molecular dynamics simulation, it appears that CETP penetrates into HDL and LDL from each end, and connects its mobile internal series of isolated hydrophobic cavities together to form a continuous tunnel, enabling the net transfer of cholesteryl moieties.

The first casualty, the CETP inhibitor torcetrapib, produced a 75% increase in HDL cholesterol levels but an actual 25% increase in MCVE with 58% greater mortality in ILLUMINATE (A Study Examining Torcetrapib/Atorvastatin And Atorvastatin Effects On Clinical CV Events In Patients With Heart Disease).³⁴⁸ These surprises were largely attributed to off-target effects of higher adrenal secretion of aldosterone and cortisol, causing an increase in hypertension and hypokalemia. Additionally, impaired endothelial function and vascular inflammation^{349,350} were evident, without any decrease in atheroma volume.

Studies on the second casualty, dalcetrapib, were stopped by Roche “[...] due to a lack of clinically meaningful efficacy” in early May, 2012. Dalcetrapib is a benzenethiol compound that binds CETP differently than does torcetrapib or anacetrapib, and is more of a modulating partial inhibitor of CETP. Dal-HEART (dalcetrapib HDL Evaluation, Atherosclerosis and Reverse Cholesterol Transport) was a program composed of six trials, of which dal-PLAQUE

and dal-VESSEL were completed, with dal-OUTCOMES incomplete at the time of termination. The dal-OUTCOMES trial was a large Phase III study evaluating the efficacy and safety of dalcetrapib as an add-on to current care for stable coronary heart disease after acute coronary syndrome using hard endpoints.³⁵¹ dal-PLAQUE was a randomized, placebo-controlled Phase IIB study in 130 patients with coronary heart disease or an equivalent, given either dalcetrapib or placebo for 2 years.³⁵² Dalcetrapib raised HDL cholesterol by 31% and ApoA-I by 10%, without changing LDL cholesterol or triglyceride levels. After 2 years, magnetic resonance imaging showed that total wall area was significantly reduced in the dalcetrapib group. Positron emission/computed tomography with ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) at 6 months showed a decrease in uptake of ¹⁸F-FDG in the dalcetrapib group, suggesting that the higher levels of HDL cholesterol were anti-inflammatory. Dal-VESSEL randomized 476 patients with coronary heart disease or risk equivalent and HDL cholesterol <50 mg/dL to dalcetrapib or placebo, followed with flow-mediated vasodilation and ambulatory blood pressure monitoring.³⁵³ After 36 weeks, HDL cholesterol rose by 31%, with no change in flow-mediated vasodilation, but mean systolic blood pressure rose by 0.6 mmHg and median C-reactive protein was 0.2 mg/L higher.¹⁴¹ Lack of improvement in endothelial function and inability to lower levels of LDL cholesterol and C-reactive protein, despite significant elevation of HDL cholesterol, together with only modest improvement in plaque through imaging, were disappointing. Analysis of dal-OUTCOMES showed no change in risk of the primary endpoint (composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, unstable angina, or cardiac arrest with resuscitation) after a median follow-up of 31 months, and was responsible for the decision to terminate development.¹⁴¹ While a number of explanations have been proposed, dalcetrapib is structurally different from anacetrapib and evacetrapib, discussed below, which may account for the results.

Anacetrapib is another agent being evaluated currently, and biochemically belongs to the torcetrapib series of CETP inhibitors.³⁵⁴ As such, it binds to CETP with a 1:1 stoichiometry and completely inhibits cholesteryl ester transfer (both heterotypic transfer from HDL to LDL, and homotypic transfer from HDL3 to HDL2) without increasing fecal elimination of either bile acids or neutral sterols. The ability of anacetrapib, niacin, and placebo to raise HDL cholesterol, and of HDL to promote cholesterol efflux, were examined in patients with dyslipidemia who were receiving standard therapy.³³⁸ HDL cholesterol rose

100% after anacetrapib and 30% after niacin treatment. Niacin increased cholesterol efflux from foam cells primarily through higher HDL cholesterol concentrations, but anacetrapib did so both by raising HDL cholesterol and through greater efflux at matched HDL cholesterol levels. Enhanced functional capacity per particle, probably related to higher ApoE and lecithin cholesterol acyltransferase per anacetrapib-HDL particle, depended on the expression of ATP-binding cassette transporters, ATP-binding cassette transporter A-1 and ATP-binding cassette transporter G-1. All preparations showed similar anti-inflammatory effects, in proportion to HDL cholesterol concentrations, and suppressed the TLR-4-mediated macrophage inflammatory response. The striking rise in HDL cholesterol and functional ability of that HDL to efflux cholesterol with anacetrapib, in addition to increases in ApoA-I and ApoA-II, was impressive.

The DEFINE (Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib) trial enrolled 1,623 patients with coronary heart disease being treated with statin drugs, randomized to anacetrapib or placebo.³⁵⁵ At the end of 24 weeks, anacetrapib increased HDL cholesterol by 138% and lowered LDL cholesterol by 40% (Table 1). The drug was well tolerated with no signs of adverse events. The major problem encountered was an 18% dropout because physicians considered that their patients' LDL cholesterol values were too low. The ability of anacetrapib to lower ApoB-containing atherogenic proteins also extended to lipoprotein(a). Merck plans to proceed with the large REVEAL (Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification) trial of patients with coronary heart disease or an equivalent being treated with atorvastatin, adequately powered to define the actions of anacetrapib on a composite of coronary death, myocardial infarction, and revascularization, but not stroke, which is scheduled to end in 2017 (<http://www.controlled-trials.com/ISRCTN48678192>).

In a study of evacetrapib, a fourth CETP inhibitor, 398 patients with either low HDL cholesterol or high LDL cholesterol were randomized to receive: placebo; evacetrapib monotherapy 30 mg/day, 100 mg/day, or 500 mg per day; or statin therapy (simvastatin 40 mg/day, atorvastatin 20 mg/day, or rosuvastatin 10 mg/day) with or without evacetrapib 100 mg/day.³⁵⁶ Coprimary endpoints were percent changes in HDL cholesterol and LDL cholesterol. As monotherapy, evacetrapib produced a dose-dependent increase in HDL cholesterol from 53.6% to 128.8% and a reduction in LDL cholesterol in the range of 13.6%–35.9%. When a submaximal

dose was added to statin therapy, LDL cholesterol fell about 50%. No signs of hypertension or excess mineralocorticoid or glucocorticoid activity were noted.

Johannsen et al used a common genetic variation in the *CETP* gene to test the hypothesis that lower CETP activity is associated with lower cardiovascular risk and MCVE.³⁵⁷ Two common single nucleotide polymorphisms of the *CETP* gene known to be associated with lower CETP mass and activity were genotyped in participants from the Copenhagen City Heart Study, in effect simulating pharmacologic CETP inhibition. In those subjects with HDL-raising alleles of *CETP*, there was a favorable lipid profile associated with lower risk of ischemic heart disease, myocardial infarction, ischemic cerebrovascular disease and stroke, and increased longevity without adverse events.

In view of these data validating the theory and practice of CETP inhibition, and lack of evidence that CETP inhibition results in dysfunctional HDL or diminished HDL-induced cholesterol efflux in the additional HDL cholesterol, there is hope that both evacetrapib and anacetrapib will eventually make a significant contribution to the treatment of dyslipidemia. Assessment of the function of the elevated HDL levels produced by CETP inhibition would be of considerable value.

Can fibrates lower residual risk?

Members of the nuclear receptor family of ligand-activated peroxisome proliferator-activated receptors (PPARs) modulate transcription of numerous target genes that encode proteins, and regulate aspects of intermediary metabolism that influence cardiovascular risk. Activation may bring about

multiple actions, depending upon the PPAR isoform, the ligand, and the tissue involved. Despite the shared properties of the three isoforms, PPAR- α , expressed in the liver, skeletal muscle, kidney, and T cells, alters genes involved with fatty acid oxidation and triglyceride-rich lipoprotein metabolism, while PPAR- γ affects those governing insulin sensitivity, adipose cell differentiation, and lipid storage. Ligands for PPAR- α include fibrates, omega-3 long chain fatty acids, and leukotriene B₄, and for PPAR- γ , ligands include free fatty acids, some eicosanoids, prostaglandins, and thiazolidinediones. Both of these PPARs are also expressed in macrophages, endothelium, smooth muscle, and the heart.

Fibrates bind to PPAR- α , heterodimerize with the retinoid X receptor, and then act upon promoter regions of genes. An associated fall in plasma triglycerides is due to increased uptake and hepatic oxidation of fatty acids, lowered hepatic production of ApoC-III, and elevated muscle cell expression of lipoprotein lipase, leading to enhanced triglyceride clearance from lipoproteins.³⁵⁸ ApoC-III normally decreases affinity of triglyceride-rich lipoproteins for their receptors and interferes with lipoprotein binding to glycosaminoglycan matrices on cell surfaces, limiting access to receptor and lipolytic enzymes. A reduction in lipoprotein ApoC-III content releases such tonic inhibition and increases lipolysis of triglyceride-rich lipoproteins by lipoprotein lipase. Lowered levels of triglyceride-rich lipoproteins may reduce the exchange of neutral lipids (triglyceride, cholesteryl ester) between HDL and VLDL. Enhanced cellular fatty acid uptake and oxidation, together with lower free fatty acid and triglyceride production, lowers VLDL synthesis.^{359,360} Hepatocyte

Table 2 Outcomes of major randomized trials using fibrates

Trial (year, duration)	Subjects, n	Treatment (versus control)	Study RRR	P-value	Subgroup criteria	Subgroup RRR (S)
Helsinki Heart Study ³⁶⁹⁻³⁷¹ (1988, 5 years)	n = 4,081 men, non-HDL-C \geq 204 mg/dL	Gemfibrozil	-34% CHD	0.02 (S)	TG >200 mg/dL, LDL-C/HDL-C >5.0	-71%
VA-HIT ^{372,373} (1999, 5.1 years)	n = 2,531 men, Secondary prevention	Gemfibrozil	-22% CVD	0.006 (S)	Diabetes	-34%
BIP ³⁷² (2000, 6.2 years)	n = 3,090, men and women, Secondary prevention	Bezafibrate (resin used by some)	-9.4% CHD	0.24 (NS)	TG >200 mg/dL, HDL-C <35 mg/dL	-42%
FIELD ^{306,375,308,309} (2005, 5 years)	n = 9,795, men and women, diabetes, 22% had a prior CHD diagnosis	Fenofibrate monotherapy (statin used by some)	-11% CVD	0.16 (NS)	TG \geq 200 mg/dL, HDL-C <40 mg/dL (men) HDL-C <50 mg/dL (women)	-27%
ACCORD ^{307,376,377} (2010, 4.7 years)	n = 5,518 men and women, diabetes, 37% had prior CV events	Fenofibrate + simvastatin versus simvastatin	-8% CVD	0.26 (NS)	TG \geq 204 mg/dL, HDL-C \leq 34 mg/dL	-31%

Abbreviations: n, patient number in original trial; ACCORD, Action to Control Cardiovascular Risk in Diabetes; BIP, Bezafibrate Infarction Prevention; CV, cardiovascular; RRR relative risk reduction; S, P-value significant; NS, P-value not significant; CVD, cardiovascular disease; CHD, coronary heart disease; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; VA-HIT, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.

production of ApoA-I and ApoA-II raises HDL cholesterol, and ATP-binding cassette transporter A-1 and scavenger receptor class B type 1 are upregulated to increase reverse cholesterol transport. Simultaneously, the expression of cytokines, chemokines, adhesion molecules, interleukin-1 β , C-reactive protein, matrix metalloproteinases, and RAGE falls, along with inhibition of proliferation and migration of vascular smooth muscle cells. Nonlipid actions include a reduction in uric acid and fibrinogen levels. Fibrates increase the affinity of LDL for the hepatic LDL receptor, and may lower LDL cholesterol concentrations modestly. These pleiotropic actions of fibrates decrease plasma triglyceride and small dense LDL concentrations, raise HDL cholesterol levels, improve endothelial function, reduce myocardial ischemic injury, and are generally anti-inflammatory and atheroprotective.^{361–363} Specifically, endothelial function is enhanced due to increased expression and activity of nitric oxide synthase,³⁶⁴ and in macrovascular endothelium by inhibition of signaling in the activator protein-1 and NF- κ B pathways to quell inflammation.^{365,366} Most recently, fenofibrate has been found to depress expression of endothelin-1, not only through PPAR α -dependent transcriptional induction of the Krüppel-like factor 11 repressor, but also by PPAR α -independent inhibition of glycogen synthase kinase-3 activity.³⁶⁷ Since endothelin-1, a vasoconstrictor produced by microvascular and macrovascular endothelium, is overexpressed in diabetics, these alterations in pathways may clarify the actions of fenofibrate upon blood vessels and lead to therapeutic targets.

Overall, in patients with hypertriglyceridemia, fibrates lower triglycerides by 15%–50% (to a greater extent when baseline levels are high), raise HDL cholesterol by 9%, and reduce LDL cholesterol by 8%.³⁶⁸ Although several randomized trials have been conducted to delineate the clinical benefits of fibrates (Table 2), their precise roles in therapy remain clouded. The Helsinki Heart Study was a 5-year, double-blind study in 4,081 asymptomatic men with non-HDL cholesterol ≥ 5.2 mmol/L (200 mg/dL) randomized to gemfibrozil or placebo.^{369,370} There was a reduction of 34% in the incidence of coronary heart disease, but no difference in all-cause mortality was observed. An open-label, 18-year follow-up found a 23% reduction in mortality. Moreover, patients with BMI and triglyceride levels in the highest tertiles had a 71% lower relative risk of coronary heart disease mortality, a 33% lower risk of all-cause mortality, and a 36% lower cancer-associated mortality.³⁷¹

VA-HIT (the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial) randomized 2,531 men with

coronary heart disease, HDL cholesterol ≤ 1.0 mmol/L (40 mg/dL), and LDL cholesterol ≤ 3.6 mmol/L (140 mg/dL) to either gemfibrozil 1,200 mg/day or placebo, and followed them for a mean of 5.1 years. In the treated group, HDL cholesterol rose by 6%, triglycerides fell 31%, and LDL cholesterol remained unchanged. These changes were accompanied by a 22% reduction in the primary end point, the combined incidence of nonfatal myocardial infarction and CHD death, during the follow-up period.^{372,373}

The Bezafibrate Infarction Prevention study was a double-blind trial in 3,090 patients with prior myocardial infarction or stable angina randomized to receive either bezafibrate 400 mg daily or placebo, followed for 6.2 years.³⁷⁴ The drug lowered triglycerides by 21% and raised HDL cholesterol by 18% in the treated arm, but the primary endpoint of a significant reduction in fatal and nonfatal myocardial infarction or sudden death was not achieved. However, a post hoc analysis in a subgroup with baseline triglycerides ≥ 200 mg/dL (2.26 mmol/L) reported the cumulative probability of attaining the primary endpoint was 39.5%.

The first study to address the hypothesis that fibrates are beneficial in patients with insulin resistance syndromes and/or high triglyceride/low HDL cholesterol levels, the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial, enrolled 9,795 participants with type 2 diabetes and total cholesterol < 6.5 mmol/L (251.3 mg/dL); fenofibrate 200 mg was administered to those randomized to treatment.³⁰⁶ While patients taking statins were not recruited, statin treatment was permitted during the trial, which may have affected outcomes. There was a nonsignificant change in the primary endpoint of nonfatal myocardial infarction and coronary heart disease mortality after 5 years, although the microvascular benefit (albuminuria/retinopathy) was impressive. On the basis of FIELD, fenofibrate could not be recommended,³⁷⁸ although benefits were more likely in patients with metabolic syndrome, particularly those with significant hypertriglyceridemia.³⁷⁵ Subsequent analysis suggested that in patients with type 2 diabetes and mild–moderate renal impairment, additional reductions in cardiovascular mortality may be possible, despite prior concern about rising creatinine levels and possible adverse renal effects.^{308,309}

The ACCORD-Lipid (Action to Control Cardiovascular Risk in Diabetes-Lipid) study was designed to determine if a fibrate-induced reduction in triglyceride/rise in HDL cholesterol improved cardiovascular outcomes when given to diabetics being treated with statin drugs. Participants were high risk type 2 diabetics being treated with simva-

statin, randomized to either fenofibrate (with simvastatin) or placebo (simvastatin alone).^{307,376} In patients receiving fenofibrate, triglyceride levels fell by 25.6% and HDL cholesterol levels rose by 8.4%. In those receiving simvastatin alone, triglyceride levels fell 10.0%, whereas HDL cholesterol rose 6.0%. There was no difference between the groups in terms of the primary outcome: a composite of the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Significantly, in a subgroup of participants with baseline values of triglyceride ≥ 2.3 mmol/L (204 mg/dL) and HDL cholesterol ≤ 0.8 mmol/L (34 mg/dL), those receiving fenofibrate enjoyed a 31% reduction in MCVE compared with those who received simvastatin alone (Adult Treatment Panel III guidelines define triglyceride ≥ 2.3 mmol/L [200 mg/dL] as high, and HDL cholesterol ≤ 1.0 mmol/L [40 mg/dL] as low). Importantly, although the ACCORD-Lipid study was “negative” for the general population, the subset of patients with atherogenic dyslipidemia did indeed benefit. Overall, in ACCORD-Lipid, about 17% of the participants were appropriate for fibrate therapy, diluting the effect of fibrate therapy. This hypothesis was confirmed in a small subgroup of patients from the same trial, in which postprandial ApoB-48 levels were further reduced by fenofibrate only in statin-treated patients with atherogenic dyslipidemia.³⁷⁷ These recent data are consistent with the view that triglyceride-rich lipoproteins may be responsible for residual risk in diabetic patients, and agree with similar findings from post hoc subgroup analyses performed from the Bezafibrate Infarction Prevention, Helsinki Heart Study, and FIELD studies. In addition, they support Adult Treatment Panel III clinical guidelines that fibrates should be reserved for statin-treated patients with high triglyceride levels and low HDL cholesterol levels, although the definitions differ (Table 2).

In a meta-analysis of 18 randomized controlled trials (including six studies in diabetic patients) totaling 45,058 participants, fibrate administration produced a 10% relative risk reduction for MCVE ($P = 0.048$), 13% relative risk ($P < 0.0001$) in coronary events, 19% relative risk ($P < 0.0001$) for nonfatal coronary events, and a 12% relative risk ($P = 0.25$) for revascularization, without significant reductions in risk for cardiac or all-cause mortality, sudden death, or stroke.³⁷⁹ Risk for progression of albuminuria was lowered by 14%, and rises in serum creatinine levels were frequent. In a meta-analysis which included the major fibrate trials mentioned above, for subgroups with triglycerides ≥ 5.28 mmol/L (204 mg/dL) and HDL cholesterol ≤ 0.879 mmol/L (34 mg/

dL), totaling 2,428 patients receiving fibrates and 2,298 placebo, the odds ratio of an MCVE was 0.65 (95% CI 0.54–0.78).³⁸⁰ Another meta-analysis, using a definition of atherogenic dyslipidemia of triglycerides > 5.17 mmol/L (200 mg/dL) and HDL cholesterol < 1.03 mmol/L (40 mg/dL) reported the greatest risk reduction in those with high triglycerides (relative risk, 0.75) and both high triglycerides and low HDL cholesterol (relative risk, 0.71), with none in the group with neither high triglycerides nor low HDL (relative risk, 0.96).³⁸¹ These results resonate with additional data³⁸² and have been synthesized into a cohesive view supporting consideration of fenofibrate or bezafibrate as an add-on therapy with statin drugs to reduce residual risk in patients with atherogenic dyslipidemia.³⁸³

Bezafibrate, unavailable in the US, has a different spectrum of action from fenofibrate, producing a greater elevation in HDL cholesterol, while manifesting additional PPAR- γ properties, such as slowing progression of impaired glucose tolerance to diabetes, and decreasing plasma glucose and HbA_{1c} concentrations.³⁸⁴ A significant rise in adiponectin levels is associated with bezafibrate therapy. Although theoretical at present, use of bezafibrate could prove useful in attenuating the diabetogenic actions of statin drugs. Balanced dual PPAR α /PPAR- γ agonists, such as aleglitazar, were believed to have the potential to improve outcomes in patients with acute coronary syndrome or prevent macrovascular complications in individuals with type 2 diabetes. Such expectations have not been realized with this agent, however, since Roche halted the investigation of aleglitazar following the results of a regular safety review of the AleCardio Phase III trial due to safety signals and lack of efficacy.³⁸⁵

To delineate whether fibrates were of overall benefit in patients with chronic kidney disease, in view of prior reports documenting reductions in renal blood flow and glomerular filtration rate,³⁸⁶ Jun et al conducted a systematic review and meta-analysis of 10 studies which included 16,869 participants.³⁸⁷ In patients with mild–moderate chronic kidney disease, fibrates lowered triglycerides and raised HDL cholesterol significantly. In diabetic patients, fibrates lowered the progression of microalbuminuria by 14%, but serum creatinine rose by about 25%, without increasing progression to end-stage kidney disease. In participants with an estimated glomerular filtration rate of 30–59.9 mL/min/1.73 m², fibrates decreased the risk of nonfatal MCVE by 30% and the risk of cardiovascular mortality by 40%, but not all-cause mortality. The authors concluded that fibrates reversibly increase serum creatinine, but these acute changes did not translate into major changes

in renal outcomes. One potential explanation may be that fibrates activate PPAR receptors that decrease vasodilatory prostaglandins, transiently reducing glomerular filtration rate with no long-term deterioration in renal function.^{388–390} The results of this study reduce concerns about long-term risk in patients with kidney disease and are encouraging.

While the focus is clearly upon “normalizing” high triglyceride/low HDL cholesterol with fibrates,³⁹¹ the mechanisms of any resulting cardiovascular protection remain unsettled. Lipoprotein changes not reflected in standard lipid profiles, changes in HDL quality, cholesterol efflux, homocysteine, and the pleiotropic anti-inflammatory, antioxidant, antithrombotic, proendothelial, antiapoptotic, and adipokine-modifying actions of PPAR α receptor activation continue to be explored.^{392,393} The FIRST (Fenofibric Acid on Carotid Intima-Media Thickness in Patients with Type IIb Dyslipidemia with Residual Risk in Addition to Atorvastatin Therapy) trial will investigate the effect of fenofibrate upon carotid intima-media thickness and LDL particles in patients taking statins with controlled LDL cholesterol levels, but with low HDL cholesterol and high triglycerides.³⁹⁴

The uncertain role of fibrate therapy has generated controversy and calls for a reassessment with fresh clinical data. The results of some of the studies cited in Table 2 were skewed by the use of older fibrates applied to patient care in an earlier era. Clofibrate became unavailable because of safety concerns, gemfibrozil–statin interactions are limiting, the practice of medicine has changed markedly, and the use of blunt surrogates (triglycerides, HDL cholesterol, LDL cholesterol) in place of hard cardiovascular outcomes is no longer acceptable. In addition, the extent and pattern of utilization of fibrates are not matched by the strength of the evidence.^{305,395,396} About 18 months after the ACCORD-Lipid trial, the US Food and Drug Administration informed that fenofibrate had not been shown to lower the risk of heart attack or stroke, and required the manufacturer of a US brand to conduct another study in high risk patients being treated with statins.³⁹⁷ This action, supported by the advisory panel,³⁹⁵ occurred amid further unease about major adverse cardiac events in female diabetics taking delayed-release fenofibric acid and simvastatin. In summary, although current data indicate a potential role for fibrates in patients with atherogenic dyslipidemia, especially with high triglycerides, and perhaps in diabetics with renal disease,³⁸⁷ the details remain unclear and the evidence base has been challenged. In addition to the National Cholesterol Education Program/Adult Treatment Panel III 2002 guidelines³⁹⁸ and the imminent Adult Treatment Panel IV revision, treatment

of hypertriglyceridemia is addressed in the AHA scientific statement on hypertriglyceridemia³⁰⁴ and the corresponding documents by the European Society of Cardiology/European Atherosclerosis Society³⁹⁹ and the Endocrine Society.⁴⁰⁰

Nonlipid determinants of residual risk

Smoking, obesity, sedentary lifestyle, hypertension, and hyperglycemia are traditional nonlipid risk factors that commonly coexist with dyslipidemia globally, as reported by the INTERHEART study.⁴⁰¹ Patients with nonlipid risk factors who are unidentified, incompletely managed, and/or who have poor adherence with treatment, may exhibit suboptimal responses and outcomes which may be grouped together with “residual risk”. There is also some indication that those patients with very high risk will have disproportionately greater residual risk. Failure to achieve evidence-based targets in patients is a complex and difficult multifactorial problem of ongoing concern.⁴⁰² In each category, unfortunately, there are patients with residual risk that remains untreatable despite state-of-the-art therapy.

In an attempt to define determinants of nonlipid risk from a prognostic rather than etiologic view, Mora et al⁴⁰³ reanalyzed data from the TNT study. A total of 9,251 patients with coronary heart disease and LDL cholesterol <130 mg/dL randomized to either atorvastatin 10 mg/day or 80 mg/day were followed for a median of 4.9 years with a primary endpoint of a first MCVE. While those treated with the higher dose of atorvastatin had fewer MCVE, 8.7% of those treated with atorvastatin 80 mg suffered another adverse event during a 5-year period, even though they had reached an LDL cholesterol target of 70–100 mg/dL.³¹ Because lower HDL cholesterol levels correlated with poorer prognoses, low HDL cholesterol and higher triglyceride levels have been considered significant predictors of residual risk.¹²⁸

In this reanalysis, however, the significant determinants predicting residual risk in statin-treated secondary prevention patients included only baseline levels of apolipoproteins, elevated BMI, smoking, hypertension, and diabetes. These investigators noted that in the prior TNT analysis¹²⁸ mentioned above, higher levels of HDL cholesterol were associated with fewer MCVE, but this relationship disappeared after adjustment for baseline apolipoprotein concentrations.

In patients being treated with statin drugs for primary prevention, a number of predictors for residual risk have been identified, including waist circumference, large artery elasticity index, homocysteine, and coronary artery calcification.⁴⁰⁴ In the large JUPITER trial, statin-treated patients with low LDL cholesterol but high C-reactive protein levels had

residual risk that was unrelated to either HDL cholesterol or triglyceride concentrations.^{139,140} Among secondary prevention trials, PROVE IT-TIMI 22 also failed to confirm such a relationship.⁴⁰⁵ These data all challenge the traditional belief that in patients with and without diabetes, a significant portion of residual risk arises from low HDL cholesterol, and/or low ApoA-I, high triglycerides, and small dense LDL.⁴⁰⁶

Another feature of the recent TNT analysis was a lack of association between on-treatment lipids or apolipoproteins beyond the baseline measurements.⁴⁰³ Given that lipids were stable beyond the 3-month measurement, the study found that no additional information would be added from measuring these values 1 year after therapy, lending partial support to becoming less concerned about lipids and targets.⁴⁰⁷ This apparent disagreement with the prior TNT analysis was attributed to inclusion of additional clinical risk factors in a more comprehensive multivariable model used in the current study. An editorialist, however, reviewed the advantages of monitoring lipids in patients requiring high-dose potent statins, including identification of subsequent nonadherence, lack of response due to associated comorbidities, and adverse effects.⁴⁰⁸

By demonstrating that residual risk results from incomplete treatment of nonlipid risk factors, these investigators stress the importance of a multifactorial therapeutic approach. Better outcomes might be attained by de-emphasizing lipid values once LDL cholesterol is within evidence-based targets, or treated appropriately within the population according to age and risk, and directing attention to discontinuing tobacco use, control of BMI, hypertension, and diabetes. Since the prevalence of these habits and factors is unacceptable (smoking prevalence is about 20%, with a high number of adolescents beginning smoking, and increased use of other forms of tobacco), prevalence of high BMI is about 70%, hypertension is about 35% ($\geq 140/90$ mmHg, using the 2011 American College of Cardiology Foundation/AHA guidelines, but using the 2007 AHA guidelines, an additional 5% have hypertension requiring treatment, bringing the total to approximately 40%), $<0.015\%$ of the population consumes the recommended amounts of dietary sodium and potassium, diabetes prevalence is about $>12\%$ (with 26% unaware of their diagnosis, and an additional 33% prediabetic), and the prevalence of metabolic syndrome is over 35%, there is significant opportunity for positive intervention.

Adherence and performance in risk reduction

Of all modifiable circumstances, poor adherence is frequently the “elephant in the room”, and is responsible for

considerable treatment failure grouped under the term residual risk. Adherence remains abysmal, and is frequently underestimated despite pill counting and fairly sophisticated methods of documentation.⁴⁰⁹ Improving patient adherence shares certain characteristics with improvements in physical activity and diet, in that all are behavioral modifications that remain major global health challenges, are partially effective interventions involving intensive investment of time and resources by health professionals, tend to be cost-prohibitive, and become progressively less effective over time.⁴¹⁰ Adherence failure is common in many chronic diseases, but knowing how many patients do not reach targets because of their poor adherence, or are simply not given a prescription by providers, is difficult. For instance, even though warfarin lowers the stroke risk by 68% and the death rate by 26% in patients with atrial fibrillation, a significant number of patients do not come under a physician's care, may not be prescribed evidence-based therapies after they do, and frequently discontinue treatment on their own. About 60% of these patients remain untreated, about half do not adhere to therapy, and in those who do, about half again remain outside the therapeutic range. Simply knowing that 59% of those who are treated are controlled (by rate or through conversion) and 41% are uncontrolled does not reveal the cause or details.⁴¹¹

The number of variables that affect patient adherence are large, and may be broadly classified as patient sociodemographic factors, provider characteristics, those relating to medications including complexity of dosing, the type/natural course of the illness, and the procedure used, if any. Patient adherence with statin drugs, as with most other drugs, is usually quoted as about 50%, varying between 25% and 75%.^{412–415} On the other hand, data from the Practice Innovation and Clinical Excellence outpatient registry indicate that about 22.3% of patients with obstructive coronary disease were not prescribed statins, and in those who were untreated, LDL cholesterol levels were ≥ 2.6 mmol/L (100 mg/dL).⁴¹⁶ Adherence is also time-dependent and procedure-dependent: in the first year following their procedure, patients who underwent coronary artery bypass grafting filled fewer prescriptions for secondary prevention medications, and also followed such therapies less consistently, than those who received percutaneous coronary intervention.⁴¹⁷

Although observational data have well-known limitations, analysis of the NHANES database (see below) not only offers significant information, but is convenient and permits comparisons between periods. In a cohort of 30,348 patients, the risk of events (diagnosis of coronary heart disease,

peripheral arterial disease, stroke/transient ischemic attacks, or revascularization) in participants who attained optimal lipid values (LDL cholesterol, HDL cholesterol, triglycerides) was compared with participants who failed to attain those targets.⁴¹⁸ The presence of a single abnormal lipid value slightly increased the event risk (hazard ratio 1.06; 95% CI 0.95–1.18), but two or three nonoptimal lipid levels significantly raised the risk of events (hazard ratio 1.22, 95% CI 1.08–1.37, and 1.45, 95% CI 1.24–1.68, respectively). The increasing significance of atherogenic triglyceride-rich lipoproteins, low total HDL cholesterol levels, and/or dysfunctional HDL has already been reviewed.^{289,304} These results add to the now overwhelming data underscoring the importance of addressing all risk factors simultaneously by both nonpharmacologic and pharmacologic means. Unfortunately, although an epidemiologic association between optimizing all lipid levels and lowering MCVE is evident, the extremely low numbers of patients who actually achieve control of multiple risk factors remain a major barrier.⁴¹⁹

In the randomized MI FREEE (Post-Myocardial Infarction Free Rx Event and Economic Evaluation) study, statins, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were fully covered by insurance in half the patients, but subject to a copay in the other half.⁴²⁰ Over 3 years of follow-up, the average adherence rate for each of the drugs in the no-copay group was 49%, but 35.9% in the copay group. After 1 year, only about 10% of patients without a copay were still taking all of the drugs as prescribed. Probably because of the paltry difference in adherence between groups, statistically significant improvement in the primary outcome, ie, the rate of first MCVE and revascularization combined, was lacking, with 17.6% per 100 person-years without a copay versus 18.8% with a copay. Given that full adherence was defined as “medication possession of over 80%”, actual adherence may have been even lower. Even so, overall expenses were lower in the no-copay group. Prior emphasis has been on physician compliance at the time of discharge, and then attributing poor adherence, in part, to drug cost, but in MI FREEE, patient behavior alone was clearly responsible.

As far as physician compliance with current guidelines for treating chronic stable angina is concerned, the impression continues that optimum medical therapy is woefully underutilized, in terms of both quantity and quality,⁴²¹ and that guidelines⁴²² are not being followed. In patients with symptomatic stable coronary heart disease, <50% of patients undergoing coronary angiography were treated with

optimum medical therapy, and two thirds were discharged on optimum medical therapy after percutaneous coronary intervention.⁴²³ In one registry, just 11% of patients with stable coronary heart disease undergoing cardiac catheterization were receiving routine medical therapy.⁴²⁴ Shortfalls in prescribed therapy are beyond the scope of this review and are discussed elsewhere.^{425,426} Apart from diagnostic coronary angiography and subsequent percutaneous coronary intervention, if one examines both adherence and attainment of risk factor goals in a mixed population of coronary heart disease patients in the “real world”, the number of patients eventually remaining undertreated becomes even more revealing. Using NHANES data for 2005–2006, among coronary heart disease survivors, 38% received angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, 58% received beta-blockers, 60% received lipid-lowering agents, and only 22% received all three therapies.⁴²⁷ About 57% reached an LDL cholesterol <2.6 mmol/L (100 mg/dL), 68% attained a blood pressure goal <140/90 mmHg, 22% remained smokers, and if diabetic, 67% achieved an HbA_{1c} < 7. Only 12% of the patients reached all four goals. A recent update on physician performance using the AHA Get with the Guidelines-Coronary Artery Disease registry reveals a marked improvement in inpatient care with respect to use of aspirin during the initial 24 hours, discharge with aspirin and beta-blockers, discharge with statin drugs, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients with low ejection fractions, and efforts to discourage tobacco use.⁴²⁸ Predictors of negative patient adherence after discharge included age, female sex, heart failure, chronic kidney disease, chronic dialysis, atrial fibrillation, and noninterventional hospitals. In spite of these data, large obstacles remain concerning patient adherence.

While only half the patients who qualify receive statin treatment, in those who do, the cross-sectional Lipid Treatment Assessment Project 2 study reported that about 70% now reach their goals in the US, which is chiefly attributed to greater use of high-potency statins.⁴²⁹ However, only about 29% of those at high risk reach the current goal of LDL cholesterol \leq 1.81 mmol/L (70 mg/dL). In one series of mixed primary and secondary prevention patients treated for 36 months in a managed care setting, 78% failed to attain optimal values of LDL cholesterol, HDL cholesterol, and triglycerides.⁴³⁰ The latest data (from NHANES 1988–1992 and 2-year cycles from 1999 to 2008) show that improvements in population cardiovascular health lag well behind those that are required.⁴³¹

In Canada and the European Union, the DYSIS (DYSlipidemia International Study) investigators found that 48.2% of primary and secondary care patients did not attain LDL cholesterol goals.⁴³² Attainment of guideline-recommended targets was assessed in high risk secondary prevention patients in the STABILITY (STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY) study, and the majority did not achieve their goals.⁴³³ Only 29% reached an LDL cholesterol <2.6 mmol/L (100 mg/dL). In the recent ASPIRE-2 Action on Secondary Prevention through Intervention to Reduce Events (PREVENT) trial in the UK, the prevalence of total cholesterol \geq 4 mmol/L (157 mg/dL) was 52.6% in patients with coronary heart disease and 78.7% in high risk patients.⁴³⁴ Laforest et al⁴³⁵ report that in patients treated with statins in France, at least one dyslipidemia persisted in 50.8% of all patients and in 71.1% of high risk patients. Further, among those with high cardiovascular risk, abnormal levels of HDL cholesterol and/or triglycerides were as prevalent as high LDL cholesterol values, suggesting that addition of agents targeting low HDL cholesterol and/or high triglyceride values might deserve attention. In France, as in the European Union and North America, only a portion of remaining abnormal values are due to incomplete management.⁴³⁶ In the US, persisting low HDL cholesterol levels are found in 67% of patients treated with statins for coronary heart disease or risk equivalents.⁴³⁷

As discussed, improvement in achieving guideline targets with other risk factors, particularly BMI, hypertension, and diabetes, will assist in lowering residual risk.¹³⁷ In hypertensive patients, even though medication lowers the risk of stroke by 30%–40% and of myocardial infarction by 25%, 60% of patients stop medication within the first year, and of those continuing, adherence again varies between 20% and 50%.^{438–440} About 35% of those with hypertension fail to receive care, and of those that do, approximately 48% are controlled, with as many as 75% failing to reach targets.⁴⁴¹ Although now decidedly improved, clinical inertia, in terms of not beginning or intensifying treatment when published goals remain unmet, continues to be substantial.^{442,443} Similar data are found in another important therapy, ie, only 41% of women who meet the criteria for use of aspirin in primary prevention and only 48% of those meeting the criteria for its use in secondary prevention actually take aspirin.⁴⁴⁴

Reduction of risk factors in diabetics is particularly disappointing. In one series of diabetics undergoing elective cardiac catheterization, 21% had HbA_{1c} <7%, 52% had an LDL cholesterol <2.59 mmol/L (100 mg/dL), 24% had triglycerides \geq 2.26 mmol/L (200 mg/dL), only approximately

Table 3 Use of four evidence-based agents in secondary prevention in the PURE study⁴⁵⁰

Percent of individuals	Statin drugs	Antiplatelet drugs	β -blockers	ACE inhibitors or ARB
Low income	3.3	8.8	9.7	5.2
High income	66.5	62.0	40.0	49.8
All	14.6	25.3	17.4	19.5

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; PURE, Prospective Urban Rural Epidemiological.

20% had normal HDL cholesterol levels, 10% had their blood pressure controlled to <130/85 mmHg, and 11% had a BMI <25. Just one patient (0.4%) had all modifiable risk factors optimally controlled.⁴³¹ Disregarding differences in definition for the moment, of diabetics participating in NHANES 2003–2006, 57% achieved an HbA_{1c} <7%, up from the prior value of 49% in NHANES 2001–2002.⁴⁴⁵ In a different analysis of NHANES 2001–2002 data, failure to reach targets was as follows: 50.2% for HbA_{1c}, 64.6% for LDL cholesterol, 48.6% for triglycerides, and 53.0% for blood pressure.⁴⁰⁶ All told, just 5.3% of men and 12.7% of women were simultaneously at target for HbA_{1c}, LDL cholesterol, and blood pressure. The distances from goals were also impressive. Among diabetics, the prevalence of dyslipidemia is about 70%, hypertension about 75%, overweight or obesity approximately 70%–80%, and both hypertension and dyslipidemia affect about 66%.^{446,447} Only 12% of diabetics simultaneously achieved targets for HbA_{1c}, blood pressure, and LDL cholesterol in the NHANES 1999–2006 database.⁴²⁷ Based on 2003–2006 NHANES data, many patients with type 2 diabetes did not appear to be at high Framingham risk, with about 23% at low risk, 17% at intermediate risk, and 60% at high risk. In the low risk group, over 50% filled the criteria for metabolic syndrome and 7% suffered from chronic kidney disease, raising the high risk total to 87%.⁴⁴⁸ Again, less than 13% of all diabetics achieved all three risk goals: HbA_{1c} (less than two thirds under control), blood pressure (about 30% under control), and LDL cholesterol (less than 50% under control), regardless of risk group.⁴⁴⁸ These investigators later estimated that if these composite risk factors were pursued aggressively in the US, almost one million fatal and nonfatal myocardial infarctions and sudden cardiac deaths could be avoided over 10 years. If less stringent guideline targets were achieved in these three parameters, about 618,100 MCVE would be avoided, along with 32% of events in men and 39% in women. These numbers may be underestimated because some of the data considered were older. The latest NHANES

data that included 2007–2010 showed significant improvements from 1988 to 1994. About 52.5% of individuals with diabetes achieved an $HbA_{1c} < 7.0\%$ (< 53 mmol/mol); 51.1% achieved blood pressure $< 130/80$ mmHg; 56.2% achieved LDL < 2.59 mmol/L (100 mg/dL); and 18.8% achieved all three ATP-binding cassette transporters. Statin use increased between 1988 and 1994 (4.2%) and between 2007 and 2010 (51.4%, $P < 0.01$).⁴⁴⁹

Looking at performance comprehensively by examining the use of secondary prevention medications that are evidence-based rather than prevalence of risk factors or extent of their reduction, the PURE (Prospective Urban Rural Epidemiological) study assessed rates of coronary heart disease and stroke and use of drugs with proven utility.⁴⁵⁰ In patients with known coronary heart disease, such agents include beta-blockers, angiotensin-converting enzyme inhibitors, statins, and antiplatelet agents. In patients with stroke, lowering blood pressure with diuretics, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and use of antiplatelet drugs and statins is accepted. The PURE investigators, led by Salim Yusuf, enrolled 153,996 adults from urban and rural areas in countries stratified into four groups based upon income, and compared the use of these medications with a past history of cardiovascular disease. Use of the basic four drugs in developed high income countries was highest but somewhat over 50%, in medium income countries was about 25%–50%, and in low income countries was less than 10% (Table 3). Half of all cardiovascular patients in the world received no treatment at all. The results were termed a collective global failure because the least expensive, safest, and most effective agents were being egregiously underused. Individual factors accounted for about one third of the variation, whereas country economic status accounted for the remainder. Urban use was greater than rural, older patients were more likely to receive therapies, and females were less likely to be treated than males. The number of deaths from withholding or delaying use of statins in hospitalized stroke patients alone was alarming. The PURE data illustrate that greater use of proven combinations of simple, available therapies will result in remarkable, virtually certain improvements in cardiovascular risk without further investment in drug development, technology, or randomized clinical trials, which have a lower probability of similar success.

Lifestyle optimization and residual risk

When immersed in the molecular mechanisms responsible for producing residual risk and their modification, it is sobering

to recall that up to 85% of cardiovascular mortality and well over half of mortality from chronic disease is preventable through simple, inexpensive measures.¹³² Further, patients who follow a healthy lifestyle after 45 years may lower MCVE by 35% and all-cause mortality by 40% in as few as 4 years.⁴⁵¹ Successfully motivating patients to improve their diet, maintain a healthy weight, discontinue tobacco use, exercise more, and develop better sleep hygiene remains a formidable individual and public health challenge.^{93,452,453}

There has been a remarkable fall in cardiovascular disease mortality over the past four decades, amounting to over 60% since the mid-1960s,^{454,455} with advances in prevention and treatment contributing about equally.⁴⁵⁶ Presently cardiovascular disease still accounts for one third of deaths in the US.⁴⁵⁷ In 2009, coronary heart disease caused one in six deaths, and stroke caused one in 19 deaths, an average of one death every 40 seconds, to total 2,150 American deaths every day. The Heart Disease and Stroke Statistical Update 2013⁴⁵⁷ attributed the high prevalence and difficult control of cardiovascular disease risk primarily to poor lifestyle behaviors and factors (smoking, diet, physical activity, BMI, hypertension, dyslipidemia, and poor glucose tolerance). If Healthy People 2010 risk factor targets had been reached, predicted coronary heart disease death rates could have been lowered about 50%.⁴⁵⁸ Of the two, primary prevention produces substantially larger reductions in coronary heart disease mortality than secondary prevention.⁴⁵⁹

Some data have suggested that when common risk factors are controlled pharmacologically, perhaps 43% of MCVE would continue.¹⁴⁷ For this reason, the search for additional biomarkers of risk continues. The tacit assumption is that new markers will be able to explain, and perhaps help control, almost all cardiovascular risk. Results from the INTER-HEART study⁴⁰¹ and other supporting evidence suggest that about 90% of the risk for myocardial infarction is already being explained using traditional risk factors. Nonetheless, our current ability to predict risk remains limited and conditional, in part related to individual variation, nonlinear time courses of progression, and unpredictable environmental factors. The reality is that individual risk prediction is still far from an exact science.^{460,461}

Long-term adherence to an “ideal” lifestyle provides the greatest reduction in overall cardiovascular risk and improvement in mortality compared with other known maneuvers. As total cardiovascular risk falls, residual risk follows and becomes less of a clinical concern. Most studies compare numbers of biomarkers improved, or adherence to desirable behaviors and factors, with outcomes. However, the addi-

tional risk that remains after commonly monitored risk factors are within target ranges, with respect to desirable behaviors and factors, has not been defined. King et al⁴⁶² sought to determine the mortality benefit of adherence to five healthy lifestyle indices [at least five servings of fruits and vegetables/day, regular exercise, being nonobese (BMI 18.5–29.9 kg/m²), no current smoking, and moderate alcohol consumption] in a cohort from the NHANES III follow-up Mortality Survey. Surprisingly, 14.9% of 11,841 participants (an unusually high figure) adhered to all five healthy habits, perhaps due to the self-reporting involved in the study. Participants who had lower levels of common risk factors (categories: LDL cholesterol, C-reactive protein, and blood pressure), tended to have higher cardiovascular mortality within each low risk factor category as the number of healthy habits followed diminished from 5 to 0–1. Similarly, for patients with low values of all three common risk factors, all-cause mortality fell significantly as adherence to the number of healthy lifestyle habits rose from 0–1 to 5.

These data have several important implications concerning clinical practice. First, there is considerable cardiovascular risk that remains even when LDL cholesterol, blood pressure, and C-reactive protein are controlled. Even if these biomarkers are normal or therapeutic targets are achieved pharmacologically, “residual risk” is still substantial. Second, in participants who followed three healthy habits, adopting all five lowered risk by an additional 46%–61%, and in those who followed 0–1 healthy habits, adopting all five could have reduced risk by 65%–84%, a striking figure compared to current performance. Taken together, advising all patients, not simply those with higher risk due to abnormal LDL cholesterol, blood pressure, or C-reactive protein values, to emphasize optimal lifestyle factors and behaviors should remain a priority. This report adds to the considerable evidence supporting the AHA’s “Simple 7” approach, using primordial prevention as a fundamental and necessary core to lower cardiovascular risk in the population. One might also add to such advice that it is not too late to begin improving lifestyle in middle age.⁴⁶³

While there is great emphasis upon lifestyle modification for primordial and primary prevention, the benefit of secondary prevention is equally significant. Recent confirmation was provided in a prospective, international study of 31,546 high risk patients with cardiovascular disease or type 2 diabetes, average age 67 years, enrolled in two randomized trials evaluating the effects of antihypertensive agents.⁴⁶⁴ Using the modified Alternative Healthy Eating Index and the Diet Risk Score, the investigators explored the association of diet

quality and a primary composite outcome of cardiovascular mortality, myocardial infarction, stroke, or heart failure during a 56-month follow-up. Participants consuming the healthiest diets, as compared with those consuming the least healthy diets (highest versus lowest Alternative Healthy Eating Index quintiles), enjoyed a 35% lower relative risk of cardiovascular death, a 14% lower risk of myocardial infarction, a 19% lower risk of stroke, and a 28% lower risk of heart failure. The study is unique in its diverse population taking secondary prevention drugs, the large number of MCVE involved, documentation of a graded, protective impact of healthy eating upon hard outcomes, with an effect that was additive to the actions of medications, and use of two independent indices of diet quality, ie, the Diet Risk Score, which is an a posteriori approach, and the Alternative Healthy Eating Index, which is an a priori means of assessment. The healthiest diets, according to these risk scores, share features of the Mediterranean diet pattern, and results were consistent with other studies of the Mediterranean diet in primary⁴⁶⁵ and secondary prevention.^{466,467} While this work was observational and cannot establish causality, the agreement with numerous other large bodies of evidence and safety of the dietary advice generated, carry considerable weight.

Three additional aspects of prevention have received current attention: the high lifetime risk for cardiovascular disease, the strikingly low prevalence of ideal cardiovascular health in both children and adults, and poor lifestyle habits in children that track into adulthood.

Global scores predicting absolute risk for 10 years are advised in the current treatment guidelines, yet lifetime risk may provide a more meaningful view of the total burden. For coronary heart disease alone, lifetime risk is 48% for men and 32% for women.⁴⁶⁸ At an index age of 50 years, estimates for lifetime risk of atherosclerotic cardiovascular disease are about 50% for men and 39% for women.⁴⁶⁹ A recent analysis pooled data from five community cohorts funded by the National Heart, Lung, and Blood Institute totaling 905,115 person-years in individuals free of cardiovascular disease with optimal risk factors (blood pressure <120/80 mmHg, total cholesterol <4.65 mmol/L (180 mg/dL), no smoking, or type 2 diabetes).⁴⁷⁰ Overall, at an index age of 45 years, men and women had an estimated remaining lifetime risk for total cardiovascular disease of over 60% and 56%, respectively, good through age 95 years. Those with optimal risk factors had a significantly improved lifetime risk of >40% and >30%, respectively (index age 55, good through 85 years). Although these data indicate that good behavior may not always be rewarded, a lower risk profile in

Table 4 Unfavorable trends in heart health statistics related to poor lifestyle behaviors and factors^{457,473}

Mortality	One cardiovascular death occurs in the US every 40 seconds, amounting to over 2,150 deaths per day; cardiovascular disease accounted for 32.3% of all deaths in 2009. In the period 1999–2009, the cardiovascular disease death rate fell 32.7% and stroke death dropped 37%. Stroke is a major cause of disability. About 1% of the adult US population qualifies for the American Heart Association definition of ideal cardiovascular health or diet. ⁴⁷⁴ Over 90% of children only meet 0–1 of the five components of an ideal cardiovascular diet. Among adolescents aged 12–19 years, 0% meet all seven behaviors and factors comprising ideal cardiovascular health; as adults, this pool of high risk individuals will worsen the risk burden in the population. ⁴⁷⁵ Targeting diet quality, and achieving small improvements in a large segment of the population might produce considerable reductions in risk factors. ⁴⁷⁶ Although there are many diets capable of satisfying criteria in the definition of ideal cardiovascular health, evidence supporting the use of a Mediterranean diet pattern for primordial, primary, and secondary prevention is impressive. ^{466,467,477–481}
Salt intake	Lowering dietary sodium intake and increasing whole grain intake present the most difficult challenges. However, reducing sodium intake by 1,200 mg/day in the US would cut the annual number of new instances of coronary heart disease by 50%, myocardial infarction by 54.5%, stroke by 48.5%, and total all-cause mortality by 47.8%. ⁴⁸² Indeed, computer simulations predict a reduction of cardiovascular disease mortality of up to 17% to over 20% over a decade if the daily 1,500 mg sodium consumption recommended by the American Heart Association were achieved, amounting to an absolute saving of 500,000–1.2 million cardiovascular disease deaths, or 100,000–190,000 coronary heart disease deaths over a decade. A reduction of 40% in sodium intake could result in 25%–30% fewer deaths, and a 4% annual fall in sodium consumption over 10 years, corresponding to about 2,200 mg/day, might produce a fall in coronary heart disease/stroke mortality of 4%–10% and of total mortality by 1.5%–3%, about half the effect of the 40% reduction. ⁴⁸³
Obesity	From 1971–2004, total caloric intake among women and men rose 22% and 10%, respectively. Over 68% of adults are either overweight or obese, and over 35% are obese. Among children, 32% are overweight or obese and 17% are obese. Observational estimates link every 4 kg/m ² increase in body mass index with a 26% rise in risk for coronary heart disease, ⁴⁸⁴ but a causal analysis with three specific genes indicates that, for every 4 kg/m ² increase in body mass index, there is a 52% rise in coronary heart disease risk. ⁴⁸⁴
Smoking	Despite progress and ongoing antismoking campaigns, tobacco use remains the leading cause of preventable death and disease among adults; 21.2% of men and 17.5% of women smoke cigarettes. Most tobacco use begins during adolescence: 18.1% of students in grades 9–12 are smokers. Of all lifestyle changes, cessation of smoking is arguably the most rewarding: there is a 36% reduction in relative risk for coronary heart disease mortality among patients who stop versus those who continue. ⁴⁸⁵
Physical activity	While 21% of adults satisfy federal physical activity guidelines, this figure is based upon self-reported data. ⁴⁸⁶ About 32% of American respondents report no aerobic activity, and 60% engage in no vigorous activity. However, when accelerometer data are used to assess physical activity, only 3.8% of American adults actually perform moderate to vigorous activity ≥ 5 days/week. ⁴⁸⁷ Moreover, guidelines are basic and alone are not optimal for weight loss. Even so, about 52% of “baby boomers” in the US report no physical activity, and overall, fewer than 17% of individuals exercise sufficiently. Among 9 through 12 graders, only 28% meet current recommendations. Cholesterol and low-density lipoprotein cholesterol remain clinically important, strong risk factors for atherothrombotic disease. ^{488,489} The hypothesis strongly suggested by epidemiological studies now largely fulfills Koch’s postulates in that: increased levels predict future major cardiovascular events preclinical work establishes a causal relationship between the two; mutations in the low-density lipoprotein receptor leading to familial hypercholesterolemia and accelerated coronary heart disease which respond to statin therapy provide links between low-density lipoprotein cholesterol, cholesterol metabolism, and subsequent major cardiovascular events; and large clinical trials using statins, other hypolipidemic agents, and intestinal bypass surgery find a reduction in major cardiovascular events. Recent data from pathological and imaging studies and from tracking of risk factors from childhood to adulthood further support the central role of atherogenic apolipoprotein B-containing particles. The use of statin drugs in certain populations, particularly for primary prevention and in elderly women, remains controversial. In these instances, however, often there is even greater need to follow alternative strategies to lower risk. ⁴⁹⁰ An estimated 14% of American adults have total cholesterol ≥ 240 mg/dL. In people ≥ 45 years of age, 25% were taking statin drugs during the period 2005–2008, up from only 2% in 1988–1994. ⁴⁷³ In the period from 2005–2008, 11.4% of Americans used at least one hypolipidemic agent, but for those ≥ 65 years of age, this figure rose to 44.5%. In large part due to increased use of statins, the percentage of adults with high low-density lipoprotein cholesterol values fell from 20% in 1988–1994 to 14.6% in 2007–2008.
Hypertension	Approximately 33% of Americans have hypertension, which is a function of age and ethnicity. About 82% are aware of their condition, 75% are using antihypertensive medications, but only 53% of those have their blood pressure controlled. African-Americans have a higher prevalence of 44%, primarily attributable to a higher risk burden rather than racial differences. Of all risk factors, uncontrolled hypertension is associated with the largest adjusted population-attributable fraction for cardiovascular disease and all-cause mortality. ⁴⁹¹ In the US, hypertension contributes to nearly 1,000 deaths daily; the World Health Organization estimates that hypertension contributes to nearly 9.4 million deaths annually. The prevalence of prehypertension (untreated systolic blood pressure of 120–139 mmHg or untreated diastolic blood pressure of 80–89 mmHg and not having been told they had hypertension on two occasions) in adults is 36.3% but again varies with age and ethnicity. ⁴⁹² In American children and adolescents the prevalence ranges from 3%–5%. Progression to hypertension occurs in up to 7% of cases.

Diabetes

About 8.3% of adults have physician-diagnosed diabetes. An additional 8.2% have undiagnosed diabetes and 38.2% have prediabetes. Together, over 15% of the population with diabetes, hypertension, or dyslipidemia is undiagnosed. For each 1 mmol/L (18 mg/dL) rise in non-fasting plasma glucose levels, the hazard ratio for ischemic heart disease and myocardial infarction rises 1.18 (95% confidence interval 1.15–1.22) and 1.09 (95% confidence interval 1.07–1.11), respectively.⁴⁹² Diabetes is the sixth leading cause of death, and the presence of the disease doubles the mortality risk. The number of adults with type 2 diabetes is expected to double by 2050, and among adolescents, could quadruple during the same time period. About 16% of patients with a prior diagnosis of type 2 diabetes do not take hypoglycemic medication. Fewer than 13% of diabetics simultaneously attain goals in glycosylated hemoglobin (<2/3 controlled), blood pressure (about 30% controlled), and low-density lipoprotein cholesterol (<50% controlled).⁴⁴⁸ If these three risk factors were aggressively treated in the US, almost a million fatal and nonfatal myocardial infarctions and sudden cardiac deaths could be avoided over 10 years. Unfortunately, intensive medical management of type 2 diabetes has disappointed. The Look AHEAD (Action for Health in Diabetes) trial showed that intensive lifestyle intervention may ameliorate many intermediate biomarkers and induce a partial remission in type 2 diabetes, but these were not translated to a corresponding fall in major cardiovascular events.^{494,495} National Institutes of Health support of the Look AHEAD intervention group has been discontinued.⁴⁹⁶ As a result, primordial and primary prevention of diabetes has assumed new importance. The Diabetes Prevention Program, which showed lifestyle optimization lowered the incidence of type 2 diabetes among high risk adults by 58%, is receiving greater attention as a primary care intervention.^{497,498} with bariatric surgery as a new alternative.⁴⁹⁹

Metabolic syndrome

While over 53% of Americans have visceral obesity, the National Health and Nutrition Examination Survey (2003–2006) reported a prevalence in metabolic syndrome of about 34%, a figure which is believed to be higher now. In subpopulations, the prevalence approaches 50%. Metabolic syndrome arises chiefly from excess net energy intake leading to insulin resistance. Adipocyte enlargement raises proinflammatory cytokine expression and infiltration of fat with macrophages, creating a chronic inflammatory state, abnormal signaling, and end organ damage.

Health, nutrition, and exercise illiteracy are common, while misinformation and unrealistic expectations are the norm. About half of patients do not read at a level to understand drug labels and medical instructions, while Internet information has created distrust and even combativeness among a cadre of “difficult patients”.

Education and awareness

Individuals entering middle age raises the probability of being free of cardiovascular disease and increasing longevity. At the index age of 45 years, those persons with no risk factors lived up to 14 years longer free of any cardiovascular disease than individuals with at least two risk factors.⁴⁷⁰ Although not addressed in this study, low fitness in mid-life is also associated with raised lifetime risk for cardiovascular disease, and moreso when risk burdens are high.⁴⁷¹

The level of cardiovascular health in the US is shockingly poor, but is part of a metamorphosis in the types of diseases now prevalent as compared with yesteryear (eg, now dominated by chronic degenerative diseases rather than acute infections) and their patterns (multiple comorbidities with long incubation periods and pathogenesis rather than single deadly illnesses).⁴⁷² The situation is similar in the European Union, and worse in many low income and middle income countries. Aging of the population, greater survival from acute exacerbations of disease, and an inordinate burden of cardiovascular risk all contribute to these phenomena.

In summary, the high prevalence of traditional cardiovascular risk factors in the US population reflects an epidemic of poor lifestyles (Table 4). Data reviewed by the 2013 AHA statistical committee confirms a dismal projection.⁴⁵⁷ While there has been some improvement in control of cholesterol and hypertension, the burdens that remain are still imposing.

Table 5 Ideal cardiovascular health is defined in terms of four behaviors and three factors

Metric	Prevalence of metric in 2010
1. Absent smoking or remote (abstinence for at least 1 year)	73
2. Body mass index <25 kg/m ²	33
3. Exercising regularly (moderate intensity ≥ 150 minutes, or 75 minutes at vigorous intensity) each week	45
4. Consuming a “healthy diet”: adhering to 4–5 important dietary components: <ul style="list-style-type: none"> • Sodium intake <1.5 g/day • Sugar-sweetened beverage intake <36 oz weekly • At least 4.5 cups of fruits and vegetables/day • At least three 1 oz servings of fiber-rich whole grains/day • At least two 3.5 oz servings of oily fish/week 	<0.5%
5. Total cholesterol <5.17 mmol/L (200 mg/dL)	45
6. Blood pressure <120/80 mmHg	42
7. Fasting blood glucose <5.6 mmol/L (100 mg/dL)	58

Notes: *Other recommendations include ≥4 servings of nuts, legumes and seeds/week; ≤2 servings of processed meats/week; less than 7% total energy intake as saturated fat.

Overall, the climbing rates of obesity, metabolic syndrome, and diabetes, as well as deterioration in overall health, despite increased life expectancy, remain alarming.

In 2010, the AHA set a goal to improve cardiovascular health by 20% and reduce cardiovascular mortality by 20%, to be attained by 2020. In a scientific statement, the AHA defined “ideal cardiovascular health”⁵⁰⁰ as the absence of cardiovascular disease, four favorable behaviors (adequate exercise, a healthy diet score, absence of smoking, and BMI <25 kg/m²), and three factors [untreated blood pressure <120/80 mmHg, total cholesterol <5.17 mmol/L (200 mg/dL), and fasting blood glucose <5.6 mmol (100 mg/dL)] (Table 5). In this document, evidence for monitoring and need for primordial prevention was reviewed in detail.⁵⁰⁰

Subsequent writings have provided additional data validating the concept of ideal cardiovascular health and the usefulness of the suggested metrics to monitor progress.^{501–505} They report that the prevalence of ideal cardiovascular health is about 1%, with only 18% of Americans following the triad of AHA metrics, ie, not smoking, maintaining a BMI <25 kg/m², and exercising at moderate to vigorous intensity for at least 30 minutes on 5 days/week. Further, they confirm that the greater the number of metrics attained, the greater the improvement in surrogate biomarkers and/or outcomes. In individuals who met at least one health metric, absolute risks were 14.8 deaths per 1,000 person-years for all-cause mortality, 6.5 for cardiovascular disease mortality, and 3.7 for coronary heart disease mortality. When six or more metrics were attained, the corresponding risks were 5.4, 1.5, and 1.1.⁴⁹¹ The same significant and inverse relationship between the number of metrics satisfied and both all-cause and cardiovascular disease mortality was reported by other investigators.⁵⁰³ Additional scientific statements address the value of the concept of ideal cardiovascular health and its direction,⁵⁰⁶ and population approaches to improve lifestyle,⁴⁵² in which the evidence for a variety of strategies are reviewed and graded. Taken together, these contributions emphasize a striking benefit from following the AHA 7 metrics, and the usefulness of monitoring those metrics, since they track from young adulthood to middle age.⁵⁰⁷

Projecting current NHANES data tracking components of ideal cardiovascular health, improvement in cardiovascular health will fall short of the AHA goals, achieving an overall increase of only 6% rather than the 20% sought by 2020, largely due to the adverse effects of the dual obesity and diabetic epidemics.⁵⁰⁵ In this projection, a precipitous rise in obesity and impaired fasting glucose was predicted, accompanied by a modest decline in smoking, hypercho-

lesterolemia, and hypertension. Indeed, in 2011, the AHA estimated the prevalence of cardiovascular disease would increase by about 10% within 20 years without changes in prevention or therapies, producing an overall prevalence of cardiovascular disease in the American population of 40.5% by 2030, with individual prevalences of hypertension at 37.3%, coronary heart disease at 9.3%, heart failure at 3.5%, and stroke at 4.0%.⁵⁰⁸

Other programs, such as Healthy People 2020 and the National Prevention, Health Promotion, and Public Health Council, remain active. The Million Hearts initiative, started in 2011, aspired to prevent a million myocardial infarctions and strokes over the ensuing 5 years by synergistically aligning programs, policies, and resources.^{509–511} Central features focused upon evidence-based use of aspirin, hypertension and cholesterol control, and smoking cessation, supplemented by reductions in consumption of salt and trans fat.

One memorable observation is that when 20,000 professionals attending one recent AHA Scientific Sessions were surveyed, only ten (0.05%) satisfied the criteria for ideal cardiovascular health. Indeed, an editorial noted that transformation of behaviors, monitoring the progress of change, and correlating them with outcome improvement will require sizeable and novel strategies.⁵¹² Changes in the environment, workplace, food industry, and health policies, with legislative support, along with media participation, will be imperative.

Emphasis on personal responsibility, which is necessary, is an unpopular subject and has generated considerable opposition. Appealing to individual ownership of one's health alone has not worked. The environmental and social barriers are so great that it is unreasonable to expect motivation and individual ability to overcome them to effect behavior change. This is particularly true when environmental and social circumstances are well beyond individual control. School lunches that do not meet current dietary guidelines, the high sodium content of hospital food, and the inability of the elderly to obtain and prepare nutritious meals are in this category. Another challenge is the current model of care and guidelines based upon patients with single risk factors or illnesses, rather than multiple conditions, so frequently encountered in patients with risk factors and the elderly. Therefore, a multilevel, simultaneous consideration of both public health policy changes and individual behavior initiatives will be needed.

Global burden of cardiovascular risk

Worldwide, cardiovascular disease leads the list of causes of mortality, accounting for 17.3 million deaths annually,

a number which is expected to rise to over 23.6 million by 2030.³ In 2001, ischemic heart disease also led the list of global mortality, with 1.4 million deaths in the developed world and 5.7 million deaths in less developed countries.⁵¹³ Although reporting of cardiovascular mortality may be less than ideal,⁵¹⁴ impressive data from all sources confirm that the global burden of cardiovascular disease is increasing disproportionately, with the ranking responsible risk factors listed as hypertension (attributability, 13%), tobacco use (9%), hyperglycemia (6%), physical inactivity (6%), and overweight/obesity (3%).³ High blood pressure and tobacco smoke also account for high disability-adjusted life years (DALYs) lost globally,⁵¹⁵ while cardiovascular disease itself causes the loss of 10% DALYs in low income and middle income countries, with about 18% of DALYs lost in high income countries. Interestingly, except for sub-Saharan Africa, overnutrition/obesity is currently a greater global threat than malnutrition to both children and adults, the former now accounting for three times as many deaths as the latter. As westernization of the globe advances, death in childhood becomes rarer and life expectancy rises, but simultaneously the prevalence of obesity (which has increased 82% worldwide within 20 years, doubling in the Middle East since 1990) and risk factors soar. Those extended years are often marred by illness, pain, and disability, ie, expanded morbidity, roughly mirroring what has

been observed in America. For each 12 months of extended life, about 9.5 months is spent in good health; for individuals older than 50 years, only 7.0 months of an extended life-year are healthy ones.

Over the last decade, concern about the global epidemic of cardiovascular disease, now grouped under the category of “noncommunicable disease,” has grown considerably.^{2,516–518} Noncommunicable diseases include cardiovascular disease, chronic respiratory disease, cancer, and diabetes, and cause about 60% of all deaths;⁵¹⁹ about half of noncommunicable disease deaths are due to cardiovascular disease. About 80% of these cardiovascular disease deaths occur in low income and middle income countries, and generally at an earlier age than in developed nations. Many of the deaths are unnecessary, affecting the young and old, and the rich and poor. They are also called “lifestyle diseases”, because they respond to corrective changes in common unhealthy behaviors such as tobacco use, alcohol consumption, poor diet quality,⁵²⁰ and lack of physical activity. Epidemic globalization of cardiovascular risk is related to modernization (largely influenced by western habits), urbanization, stress, and lack of access to nutritious foods, health care services, and medications.

The United Nations passed a resolution on May 13, 2010 calling for a meeting on noncommunicable diseases that took place in September, 2011 to discuss the complex

Table 6 Proposed and supported core strategies to reduce noncommunicable diseases⁵³⁰

Suggested target	Population-based goal: reduction of prevalence	Individual goal (if included)	Considered a “best buy”	Local modification recommended*
Insufficient physical activity	10% relative reduction	–	Yes	No
Elevated blood pressure (systolic BP \geq 140 mmHg, diastolic BP \geq 90 mmHg)	25% relative reduction	–	Yes	No
High sodium intake	39% relative reduction	<5 g salt (about 2,000 mg sodium)/day	Yes	No
Tobacco use	30% relative reduction		Yes	No
Saturated fat intake	15% relative reduction in mean proportion of total energy intake	<10% of total energy intake	Yes	Yes
Obesity	50% reduction			No
Alcohol use	10% relative reduction	Reduction in excessive, hazardous, and harmful drinking	Yes	Yes
Elevated total cholesterol	20% relative reduction			No
Availability of services for prevention	50% of eligible patients receiving drugs and counseling		Yes	No
Availability of essential generic medications and basic technologies to treat major noncommunicable diseases	80% availability			No

Notes: *Modification by local member states suggested, according to the distribution of their burdens, priorities, strength of their data, and practical considerations.

Abbreviation: BP, blood pressure.

challenge of controlling the epidemic in the face of diverse social constraints and adverse economic realities.⁵²¹ During this event, which served as a catalyst to promote awareness, motivation, and inspire advocacy and future progress, a target of lowering premature mortality 25% by year 2025 was set. Additional plans for intervention followed,^{3,4,522,523} and more recently, further population-based approaches have been proposed^{453,524} including novel patient communication techniques.⁵²⁵ Unfortunately, as is well-known from weight loss programs, improving behaviors and health factors, although possible,⁵²⁶ is a most challenging endeavor, and simple, intuitive techniques may often disappoint, especially when they must be sustained.^{527,528} In addition to a comprehensive UN report setting forth the challenges in detail,³ several outstanding recent commentaries and reviews are available for the interested reader.^{517,522,523,529–532}

The Call for Action by the United Nations added to the prior core set of 10 global risk reduction targets identified by a World Health Organization technical working group. The World Heart Federation, American Heart Association, American College of Cardiology Foundation, European Heart Network, and the European Society of Cardiology recently penned an advisory setting targets for eight cardiovascular disease risk factors, with recommendations ensuring availability of essential generic medicines and basic technologies for treatment (Table 6).⁵³⁰ Those recommendations that are universally cost-effective and feasible have been termed “best buys”, whereas others might require modification because importance of risk factors and disease burden vary among nations. Overall, it has been suggested that substantial underuse of proven therapies and overuse of ineffective ones need to be reversed by targeting barriers, additional implementation research, and novel community intervention strategies.⁵³⁴ Note that despite the fundamental importance of obesity, reversal may not be a best buy in many countries; it is regarded as a prevalent product of culture, hamstrung by misbeliefs, intractable behavior patterns, and environments that have not responded to modification thus far.^{535,536}

Nonetheless, additional population-based and environmental strategies have been offered. These include subsidies, taxation, environmental restructuring, and resetting default health options to a positive position.⁹³ For tobacco use, providing more health information and warnings, bans on advertising and promotion, smoke-free environments, and taxation are possible. For alcohol abuse, restricted access, advertising control, and tax increases might be appropriate. For food, agreements with industry

or legislation, and public information campaigns have been proposed.

Current evidence now compels a fresh, intensive, comprehensive approach of unprecedented proportions to slow the current oppressive increase in cardiovascular risk. The elements of success and failure of past programs, especially those with high visibility, such as the antismoking and anti-acquired immune deficiency syndrome campaigns, must be dissected and another forged with even greater vigor and resolve to combat obesity and other risk factors. New public health policies, with significant social and food industry changes, will require extraordinary skill and advocacy to enact and implement.

Conclusion

Residual risk is common, underappreciated, and underrecognized, and is generated not only by incomplete and undressed lipoprotein moieties, but also by nonlipid factors, some of which may be eliminated with current and novel therapies. Although many biochemical processes may contribute to, or protect against, the progression of atherosclerosis, LDL cholesterol plays a central role in the former, and HDL cholesterol a role in the latter. However important, pharmaceutical control of lipids is only a portion of the total management of patients with dyslipidemia. Even though intensive statin therapy in high risk patients is well accepted, the residual risk that persists remains appreciable. Some residual risk is attributed to low levels of HDL cholesterol and/or high concentrations of triglyceride and lipoprotein remnants. A low level of HDL cholesterol remains an undisputed risk factor. The HDL hypothesis, however, will need adjustment, since recent evidence suggests that raising HDL cholesterol per se may not produce improvements in outcome, and quality of HDL may be a more suitable target than HDL.⁵³⁷ Healthy HDL protein is generally cardioprotective, but modified HDL proteins, particularly those carrying more ApoC-III, may increase risk. Both protective and harmful effects are independent of HDL cholesterol concentrations. Abandoning HDL-based therapies may be premature, since they have the potential to add value to the cardiologist's armamentarium at a crucial time. More information is required about the relative contributions of various properties of healthy and diseased HDL to atheroprotection, particularly macrophage cholesterol efflux, protection of LDL from oxidation, anti-inflammatory actions, and direct endothelial effects. A rapid, robust, and inexpensive way to assess HDL function in clinical settings would be helpful.

Of the pharmacologic agents available to raise HDL cholesterol other than statins, there are niacin, fibrates, and

thiazolidinediones. In view of the AIM-HIGH and HPS2-THRIVE studies casting doubt on the effectiveness of niacin, lack of evidence for use of fibrates with simvastatin to improve cardiovascular outcomes in diabetic patients with triglycerides ≤ 27.78 mmol/L (500 mg/dL) or without the atherogenic triad, and recent concerns regarding the adverse reactions of thiazolidinediones, such as bladder cancer, weight gain, macular edema, and fluid retention with heart failure with pioglitazone, and well publicized warnings regarding rosiglitazone in patients with myocardial ischemia and heart failure, the pharmaceutical options available to lower residual risk seem to be decreasing. For each method of raising HDL cholesterol, demonstration of antiatherosclerotic efficacy with hard endpoints is now necessary. Nonprescription choices to raise HDL cholesterol include weight loss, dietary changes, tobacco avoidance, aerobic exercise, and prudent use of alcohol.

Inhibition of CETP, which exchanges cholesteryl ester from HDL for triglycerides in ApoB-containing particles, is an effective means of raising HDL cholesterol, and depending upon the inhibitor used, may also decrease LDL cholesterol. However, the number of smaller, cholesterol-poor HDL particles needed to remove tissue cholesterol may be lowered as well. Thus far, two CETP inhibitors, evacetrapib and anacetrapib, still under development, appear to be promising agents, to be used either alone or as add-ons to statin therapy.

Non-HDL cholesterol is a robust, accurate, useful, and practical marker of atherogenic risk, offering several advantages as a primary therapeutic target. At every triglyceride level, non-HDL cholesterol outperforms LDL cholesterol.

An examination of the causes of residual risk leads well beyond the pharmacologic limitations of statin drugs, which have improved patient outcomes strikingly, but extend to other risk factors, including: patient-related beliefs, factors, and behaviors, most notably lack of adherence; to habits and customs related to health systems; and to societal priorities, including environmental, educational, and legislative issues with respect to lifestyle promotion.^{93,452}

Despite the remarkable decrease in the incidence of acute myocardial infarction and reduction in coronary heart disease mortality, together with technologic advances in evaluation and management of heart disease over recent years, cardiovascular diseases remain among the leading causes of death. A perfect storm of rising burden of cardiometabolic risk is predicted as the age of the population increases, the epidemics of obesity and diabetes progress, the number of adolescents

and young adults with obesity, diabetes, and microvascular complications mature, and additional segments of the population are added to the health care system. As the total risk and age burdens rise, the associated fraction of residual and untreatable risk may increase disproportionately, allowing evidence-based treatment goals to distance further from reach, even while prescription frequency and efficiency grow.

For these reasons, addressing lifestyle habits and behaviors appears to be even more attractive than in the past. Pharmacologic reduction in residual risk is currently difficult, uncertain, and incomplete, whereas prevention, when achieved, produces reliable, consistent success. In order to reverse current trends and improve cardiovascular health and outcomes, primordial prevention is necessary, in addition to other evidence-based intensive pharmacologic and invasive therapies.

Acknowledgment

The author wishes to thank Michelle Delaney for her astuteness, computer skills, untiring assistance, and valuable suggestions during the preparation of this manuscript.

Disclosure

The author reports no conflict of interest in this work.

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