REVIEW

Primary prevention of coronary heart disease: integration of new data, evolving views, revised goals, and role of rosuvastatin in management. A comprehensive survey

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Abstract: A recent explosion in the amount of cardiovascular risk and incipient, undetected subclinical cardiovascular pathology has swept across the globe. Nearly 70% of adult Americans are overweight or obese; the prevalence of visceral obesity stands at 53% and continues to rise. At any one time, 55% of the population is on a weight-loss diet, and almost all fail. Fewer than 15% of adults or children exercise sufficiently, and over 60% engage in no vigorous activity. Among adults, 11%–13% have diabetes, 34% have hypertension, 36% have prehypertension, 36% have prediabetes, 12% have both prediabetes and prehypertension, and 15% of the population with either diabetes, hypertension, or dyslipidemia are undiagnosed. About one-third of the adult population, and 80% of the obese, have fatty livers. With 34% of children overweight or obese, prevalence having doubled in just a few years, type 2 diabetes, hypertension, dyslipidemia, and fatty livers in children are at their highest levels ever. Half of adults have at least one cardiovascular risk factor. Not even 1% of the population attains ideal cardiovascular health. Despite falling coronary death rates for decades, coronary heart disease (CHD) death rates in US women 35 to 54 years of age may now be increasing because of the obesity epidemic. Up to 65% of patients do not have their conventional risk biomarkers under control. Only 30% of high risk patients with CHD achieve aggressive low density lipoprotein (LDL) targets. Of those patients with multiple risk factors, fewer than 10% have all of them adequately controlled. Even when patients are titrated to evidence-based targets, about 70% of cardiac events remain unaddressed. Undertreatment is also common. About two-thirds of high risk primary care patients are not taking needed medications for dyslipidemia. Poor patient adherence, typically below 50%, adds further difficulty. Hence, after all such fractional reductions are multiplied, only a modest portion of total cardiovascular risk burden is actually being eliminated, and the full potential of risk reduction remains unrealized. Worldwide the situation is similar, with the prevalence of metabolic syndrome approaching 50%. Primordial prevention, resulting from healthful lifestyle habits that do not permit the appearance of risk factors, is the preferred method to lower cardiovascular risk. Lowering the prevalence of obesity is the most urgent matter, and is pleiotropic since it affects blood pressure, lipid profiles, glucose metabolism, inflammation, and atherothrombotic disease progression. Physical activity also improves several risk factors, with the additional potential to lower heart rate. Given the current obstacles, success of primordial prevention remains uncertain. At the same time, the consequences of delay and inaction will inevitably be disastrous, and the sense of urgency mounts. Since most CHD events arise in a large subpopulation of low- to moderate-risk individuals, identifying a high proportion of those who will go on to develop events with accuracy remains unlikely. Without a refinement in risk prediction, the current model of targeting high-risk individuals for aggressive therapy may not

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succeed alone, especially given the rising burden of risk. Estimating cardiovascular risk over a period of 10 years, using scoring systems such as Framingham or SCORE, continues to enjoy widespread use and is recommended for all adults. Limitations in the former have been of concern, including the under- or over-estimation of risk in specific populations, a relatively short 10-year risk horizon, focus on myocardial infarction and CHD death, and exclusion of family history. Classification errors may occur in up to 37% of individuals, particularly women and the young. Several different scoring systems are discussed in this review. The use of lifetime risk is an important conceptual advance, since ≥90% of young adults with a low 10-year risk have a lifetime risk of ≥39%; over half of all American adults have a low 10-year risk but a high lifetime risk. At age 50 the absence of traditional risk factors is associated with extremely low lifetime risk and significantly greater longevity. Pathological and epidemiological data confirm that atherosclerosis begins in early childhood, and advances seamlessly and inexorably throughout life. Risk factors in childhood are similar to those in adults, and track between stages of life. When indicated, aggressive treatment should begin at the earliest indication, and be continued for years. For those patients at intermediate risk according to global risk scores, C-reactive protein (CRP), coronary artery calcium (CAC), and carotid intima-media thickness (CIMT) are available for further stratification. Using statins for primary prevention is recommended by guidelines, is prevalent, but remains underprescribed. Statin drugs are unrivaled, evidence-based, major weapons to lower cardiovascular risk. Even when low density lipoprotein cholesterol (LDL-C) targets are attained, over half of patients continue to have disease progression and clinical events. This residual risk is of great concern, and multiple sources of remaining risk exist. Though clinical evidence is incomplete, altering or raising the blood high density lipoprotein cholesterol (HDL-C) level continues to be pursued. Of all agents available, rosuvastatin produces the greatest reduction in LDL-C, LDL-P, and improvement in apoA-I/apoB, together with a favorable safety profile. Several recent proposals and methods to lower cardiovascular risk are reviewed. A combination of approaches, such as the addition of lifetime risk, refinement of risk prediction, guideline compliance, novel treatments, improvement in adherence, and primordial prevention, including environmental and social intervention, will be necessary to lower the present high risk burden.

Keywords: primary prevention, cardiovascular risk, coronary heart disease, primordial prevention, rosuvastatin, JUPITER study, statin drugs, C-reactive protein, inflammation, low-density lipoprotein, high-density lipoprotein, diabetes, metabolic syndrome, Framingham risk score, Reynolds risk score, SCORE, coronary artery calcification, carotid intima-media thickness, hypertension, obesity, non-HDL-cholesterol, LDL-P, dysfunctional HDL, lifetime risk, advanced lipid testing, Bogalusa Heart Study

Introduction: the enormity of the challenge

Cardiovascular disease (CVD) claims 2,300 lives each day in the United States, averaging one death every 39 seconds. In 2006, 81 million people in America suffered with ≥ one type of cardiovascular disease. Presently one in three Americans has CVD, and 35% of all American deaths are due to the scourge.[1] Coronary heart disease (CHD) is the leading cause of death in the US and the UK: one coronary event occurs every 25 seconds in America, with 34% dying within the same year, amounting to one death every minute. On an annual basis, about 785,000 Americans have new coronary attacks, and 470,000 have a recurrence, with an estimated 195,000 first myocardial infarctions that occur silently.[1] There were about 406,351 deaths in the United States from CHD in 2007, approximately one in six of all deaths.[2] Thirty-five years ago, the number of coronary deaths was significantly higher, and the prognosis was limited by the relative dearth of technical, invasive, and pharmacological options.[3] Currently, there are about 6.2 million hospitalizations for cardiovascular disease each year in the USA, 730,000 hospitalizations for stroke, and 7.2 million cardiac and vascular procedures are performed.[4] A similar situation now exists world-wide.[5,6]

CVD now consumes 17% of the national health budget in America, where health expenditures, matching the body mass indices (BMIs), are the highest in the world. The cost of CVD in the USA has recently grown at an average annual rate of 6%, and accounts for about 15% of the rise in total medical expenditures. During the next 20 years, the prevalence of CVD will rise by about 10%, and the costs attributable to CVD will triple, simply because of demographic changes in the population. By 2030, without any change in prevention or treatment practices, it is projected that the number of people with one of more forms of heart disease will increase from 36.9% to 40.5%, to total 116 million American adults. By then, the incidence of heart failure and stroke will have each risen by ≈25%.[7]

Although the death rate from CHD has fallen, the prevalence of risk factors, especially obesity and diabetes, continues at an alarming level, actually making the above estimates conservative. The present crop of adolescents who are overweight will increase the number of obese adults an additional 5%–15% by 2035, generating another 100,000 prevalent cases of CHD. There is increasing evidence that obesity is offsetting improvements in CHD mortality,[8,9] and a recent comprehensive review by the National Research Council found that the high prevalence of risk factors, particularly obesity, was a major factor accounting for

lagging improvement in longevity in America and developed countries.[10]

Despite remarkable advances considered science fiction just a short time ago, treatment success, as cardiologists well know, remains a constant uphill struggle. The sobering figures above have prompted many epidemiologists and preventive cardiologists to suggest that changes in thinking and approach in primary prevention have been needed for some time. In contrast with the dire predictions outlined above, another pathway is possible. A rich data base,[11] including the INTERHEART study[12] and recent models,[13] suggest a refreshing, alternative direction. By lowering the prevalence of risk factors, there will be an anticipated reduction in both CVD events and cardiovascular mortality of striking proportions.[7]

Most risk factors that drive cardiovascular disease have genetic, physiologic, behavioral, and environmental components. Nonmodifiable risk factors include age, genetics, and gender. Modifiable risk factors comprise smoking, dyslipidemia, hypertension, and diabetes, with obesity and metabolic syndrome usually included. Emerging, "novel," or nontraditional risk factors for risk assessment include C-reactive protein (CRP), lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$),[14] LDL particle number (LDL-P), fibrinogen, lipoprotein (a) [Lp(a)], small, dense LDL, triglycerides (TG) and triglyceride-enriched particles, plasminogen activator inhibitor (PAI-1), interleukin-6 (IL-6), and others. Leading contenders among imaging techniques capable of refining risk prediction or improving management include measurement of carotid intima-media thickness (CIMT), coronary artery calcification (CAC), and MRI or CT coronary angiography (Table 1).

Risk factors influence the pathobiology of atherosclerosis and coronary artery disease in a continuum during a complex interaction of genetics and environmental factors throughout life. Modifying events along this long time span include lifestyle changes, primarily nutrition, exercise, stress, comorbidities, pharmaceuticals, particularly statins, percutaneous interventions, and surgery.

A significant number of pharmacological agents are now prescribed for cardiovascular risk reduction during both primary and secondary prevention, as well as during treatment of coronary heart disease (CHD). A recent paper focused on rosuvastatin, reviewing its properties and some details about use in primary prevention.[15] This complementary paper examines new data, changes in views about primary prevention, the rationale for alternative approaches, and surveys several recent proposals to improve risk stratification and clinical outcomes.

Table 1 Common tools used in cardiovascular risk assessment

Clinical evaluation: history and physical examination
Family history
Global Risk Scoring (FRS, SCORE, Reynolds)
Calculation of lifetime risk
Electrocardiogram (ECG)
Echocardiography
Stress (Exercise) electrocardiography
Myocardial perfusion imaging (MPI)
Stress (Exercise) echocardiography
LDL-C (apolipoprotein B, non-HDL-C)
HDL-C
Lipoprotein "little a" (Lp(a))
Lipoprotein fractionation (VAP, NMR)
hsC-reactive protein (CRP)
Lipoprotein-associated phospholipase A2 (Lp-PLA2)
Coronary angiography
Carotid intima-media thickness using ultrasound (CIMT)
Computed tomography for coronary calcium (CAC)
CT coronary angiography
MRI coronary angiography

Abbreviations: FRS, Framingham Risk Score; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CT, computerized tomography; MRI, magnetic resonance imaging.

Types of prevention

Prevention, although relatively unfashionable when compared to cutting-edge high-tech procedures, addresses two of the three goals of medicine: preventing disease, relief of suffering, and prolonging life. On the other hand, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) excel in relieving suffering unresponsive to medical therapy, making the combination of prevention and therapeutic procedures a complementary union of partners in a continuum of management.

Prevention may refer generally to screening and immunizations to detect, forestall, or limit serious disease. Primary prevention denotes delaying or limiting a first event in individuals who have not yet been formally diagnosed with heart disease. Usage includes individuals with risk factors, the latter commonly regarded as if they were in fact diseases themselves, since often they are simultaneously causes, surrogates, and targets for therapy. Secondary prevention seeks to prevent, postpone, or limit recurrence of a clinical event in patients who have been previously diagnosed with cardiovascular disease. The functional distinction between the types of prevention appears to be blurring.[16] For complex reasons, prevention receives ≤3% of the health care budget,[17] and prevention measures are underemployed, even in the context of a current ≈55% utilization of all recommended effective therapies.[18] Cost-ineffectiveness has been disproved for individual primary prevention techniques.[19,20] The

National Institute for Health and Clinical Excellence (NICE) in the UK estimated that a 1% population-wide lowering of cardiac risk factors would net substantial savings,[21] yet even with widespread agreement, prevention services remain low on US payers' priorities, and are similarly undervalued by the public.

Primordial prevention

Primordial prevention, a term first used by Strasser,[22] refers to individual behavioral lifestyle characteristics that achieve a level of health that does not permit risk factors to appear. The American Heart Association (AHA) incorporated the powerful principle of primordial prevention in defining "ideal cardiovascular health" as a goal in reducing cardiac and stroke mortality 20% by year 2020.[2] Ideal cardiovascular health consists of the absence of cardiovascular disease, a healthy lifestyle (sufficient exercise, a superior diet score, absence of smoking, and BMI < 25 kg/m^2), and ideal health factors (untreated normal values of blood pressure, cholesterol, and fasting glucose). These parameters, termed Life's Simple 7™, are presented in an AHA educational site, mylifecheck.org, which promotes primordial prevention (Table 2). Presentation of material is layered, clear, in language that is easily understood, and user-friendly. The AHA Goals also emphasized the need for a plant-based diet containing legumes, nuts, seeds, and minimum amounts of trans and saturated fats.[2]

Reversal of existing risk factors does not equal the degree of protection afforded by primordial prevention.[23,24] Since atherosclerosis begins at an early age and progresses

Table 2 Ideal Cardiovascular Health, defined by the American Heart Association, now known as "Life's Simple 7™", is composed of four behaviors and three factors[2,*]

1. Not smoking or quitting over 1 year ago.
2. A body mass index <25 kg/m^2.
3. Exercising at a moderate intensity $\geq$150 minutes (or 75 minutes at vigorous intensity) each week.
4. Eating a "healthy diet": adhering to four to five important dietary components
   - sodium intake $<$1.5 g/day;
   - sugar-sweetened beverage intake $<$36 oz weekly;
   - $\geq$4.5 cups of fruits and vegetables/day;
   - $\geq$three 1 oz servings of fiber-rich whole grains/day;
   - $\geq$two 3.5 oz servings of oily fish/week.
5. Maintaining total cholesterol (TC) $<$200 mg/dL.
6. Keeping blood pressure $<$120/80 mmHg.
7. Keeping fasting blood glucose $<$100 mg/dL.

Notes: *Other recommendations include $\geq$ four servings of nuts, legumes and seeds/week; $\leq$ less servings of processed meats/week; less than 7% total energy intake as saturated fat.

throughout life, primordial prevention is uniquely successful in combating CHD, but also adds protection against other degenerative diseases to reduce all-cause mortality. Dietary changes alone can produce – and completely reverse – lesions of CHD in primates[25] and intensive lifestyle programs may cause lesion regression in humans.[26] Individuals who achieve primordial prevention are uncommon, with fewer than 5% achieving ideal cardiovascular health as they approach middle life.[2] When individuals do enter middle age without risk factors, their cardiovascular protection is extraordinary and they enjoy an additional 10 years of life.[27,28] A number of recent impressive prospective studies and models support these findings, suggesting that population-based primordial prevention is capable of reducing CHD deaths to approximately 10% of the current expected rate.[8,11]

Among the strategies to lower risk are proposals involving reeducation, reorientation, and motivation of individuals so their lifestyles do not permit risk factors to develop, or slow to the extent that their lifetime risk is lowered. Weight loss of 15% or more of body weight with other dietary and lifestyle interventions, especially exercise, will drastically reduce cardiovascular risk up to 45% and simultaneously lower CRP levels.[29] School- and community-based initiatives, improvement in diet and food quality, social support, and other incentives are among the approaches available. Health, nutrition, and exercise illiteracy are prevalent, with misinformation and unrealistic expectations also common. From an intuitive and qualitative view, therefore, corrective education would appear beneficial. Overall, however, such current methods to positively influence individual behavior have been unsuccessful. A recent Cochrane review of 55 trials reported that counseling and educational programs can lower risk factor burdens modestly, but do not lower CHD events, total or CHD mortality in the general population, and are therefore not recommended or evidence-based.[30] They did find, however, that patient education and counseling may be useful in high-risk diabetic or hypertensive populations, from which the inference was made that patients with pre-existing disease benefited, but not those who were undiagnosed. Removal of education, behavioral intervention and counseling, as suggested, would leave policy decisions, largely environmental, as the remaining technique available for primordial prevention.

This report[30] uniquely disagrees with a large body of evidence that preceeded it, and is at odds with pathological data and available guidelines concerning cardiovascular risk management.[2,6,31,32] It suggests that current initiatives, such as the American Heart Association's Life's Simple 7™, will

have limited effect, and that public health policies to lower cardiovascular risk in most countries may be misguided. Ignoring patient education, as is implied, is also contrary to the Institute of Medicine's goal of a patient-centered health system[33] and simultaneously undermines a core constituent of models to improve care and patient value by allowing participation in clinical decision-making.[34] The components of patient attitudes and behavior are complex, and are of such crucial importance that further analyses, such as done by White,[35] are needed to refine future approaches.

The accompanying editorial[36] observed that there were no recent large-scale randomized controlled trials on the issue, and reviewed the pitfalls and perils involved in making educational and behavioral modification programs effective. The design, recruitment, administration (especially adherence verification), and successful completion of such a study presents enormous challenges. Funding for such a project is highly unlikely. In the absence of such randomized trials, the editorialist stressed reducing dietary salt intake, legislating for smoke-free public spaces, and exercise parks to facilitate primordial prevention. Unfortunately, these policies too have encountered obstacles. Environmental restructuring to improve health has been challenged legally, and has been considered intrusive in some venues.

Shortly thereafter, the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group published three reports that described global population-level changes in body-mass index (BMI), systolic blood pressure, and total cholesterol over three decades.[37–39] Involving 3.0–9.1 million participants over 321–960 country-years, their three studies found that obesity rates doubled between 1980 and 2008, overweight affected one in three adults, and obesity affected one in nine adults in the world. Global BMI increased on average 0.4 to 0.5 kilograms, about 0.9 to 1.1 pounds, per decade for men and women. Changes in blood pressure and cholesterol varied according to income and location, and sometimes were disparate with the rises in BMIs. Even so, the high cardiovascular disease burden in low- and middle-income countries over the next few decades was deemed dismal and an emergency.[40] The solution proposed to avert tens of millions of preventable deaths was, not surprisingly, population-based risk control.

High-risk individual model vs a population-based model

The current paradigm in both primary and secondary prevention seeks to identify individuals at high risk for cardiovascular events through screens and target them for additional evaluation, stratification, and intensive treatment. Guidelines concentrate on maximizing use of these steps to produce the greatest reduction in clinical events, quality of life, and survival. Throughout the past four decades, this approach has been rewarding, with extraordinary advances that have been reflected in large decreases in cardiovascular mortality. For example, for every 10% rise in treatments of LDL-C elevations in the population younger than 80 years, approximately 8,000 deaths could be prevented annually,[20] and for a 10% rise in hypertension therapy, about 14,000 deaths per annum would be averted. A fall in risk factors within the population accounts for about half of the lowering of death rates during the past 40 years.[41–45] Despite this improvement, death from coronary heart disease remains at the top of the list, and will also be the leading cause of death world-wide within the decade. Moreover, the recent lowering of CHD deaths has shown signs of slowing, probably due to the dual epidemics of obesity and diabetes. From a public health perspective, somewhat over 40% of CHD events occur in the 6% of the population with manifest disease, much of which is preventable with effective measures.[46]

Geoffrey Rose[47–50] a British epidemiologist, compared health consequences when individual care is given to high-risk individuals, often those who make poor lifestyle choices, compared to treating the entire population. He also addressed environmental and behavior characteristics of the population in general. Following a population-based strategy to control risk, changes in a large number of people resulted in a smaller individual benefit, and required a relatively larger political and economic change for success.[47] Cultural and regional differences, ie, "diversity", complicated implementation. Rose said "mass diseases and mass exposures require mass remedies", emphasizing that sick individuals arise from sick populations, and that the number of persons with undesirable levels of risk factors depends upon the average risk in the population.[49] He observed that the behaviors of many subjects with low risk have a greater impact upon disease prevalence than fewer individuals with high risk.[48] Treatment of high-risk individuals tended to be crisis intervention and only palliative, whereas population intervention targeted fundamental causes.

Less than 10% of the population is at high risk for cardiovascular disease, but the low to intermediate risk group is so large that most cardiovascular events will actually arise from that population.[1,47,51] As a result, 90% or more of cardiovascular events will occur in individuals with one or more risk factor, somewhat under half of the population.[52] Importantly, this subpopulation with cardiac

events would not qualify for intensive diagnosis or treatment using high-risk filters. Lowering the risk factor burden in the general population through lifestyle, environmental, and social changes would be expected to produce greater reductions in CHD risk.

High burden of cardiovascular risk
Past and future trends are unfavorable

During the last two decades, adherence to a healthy lifestyle has deteriorated significantly.[11,53,54] From 1988–2006, the prevalence of obesity increased from 28% to 36%, consumption of ≥5 portions of vegetables or fruits was nearly halved, level of physical activity also fell, while alcohol consumption rose. Patients with diabetes or heart disease also reported poor performance in these categories.

Examining 10-year trends in chronic illnesses, Paez and collaborators[55] used the prevalence of self-reported conditions during expenditure surveys, and noted that in 2005, 44% of Americans had at least one chronic disease. The number of persons with three chronic conditions rose sharply, however, when compared with the number with one illness. For persons ages 45–64 years, the prevalence of multiple chronic conditions in 1996 was 13%, and by 2005 rose to 22%. In 2010, an analysis by Health and Human Services reported 27% of the population suffered with multiple chronic illnesses.[55]

Today very few Americans are at low risk for heart disease. Continuing reports of rising prevalence of overweight and obesity not only reflect acceleration, but absolute levels are higher than ever before.[56,57] Since the data are self-reported, the actual numbers are likely worse. Even in the face of consistently rising risk, 65% of Americans rate their health as good, but overweight and obesity alone exceed this number. Over 55% of young adults have at least one CVD risk factor, and over 37% reported having ≥ two risk factors for CVD (with only 35% under control), all reflecting a dissociation between perception and reality. Indeed, the US Centers for Disease Control and Prevention (CDC) reports that Americans are now sicker than ever.[58] In Canada too, 90% of citizens report they are healthy, when actually 90% of them have ≥ one risk factor, also an apparent denial of the prevalence of risk factors.[59]

According to American Heart Association criteria, perhaps 5% of Americans were considered to have ideal cardiovascular health when the 2010 Impact Goals were presented,[2] but subsequent evaluation reveals it is actually less than 1%. If recent increases in the incidence of diabetes continue, the prevalence of diabetes in American adults,

including undiagnosed cases, is projected to rise from the present 14% to 33% of American adults by 2050.[60] Even with vigorous intervention, a significant increase in diabetes prevalence will be inevitable.[61] Clyde Yancy MD, Chief of Cardiology at Northwestern University and past president of the AHA, in an editorial about the challenges of lowering risk in the population, recently termed the cardiovascular health status in America "miserable".[62] Unfortunately, an end to the dual epidemics of obesity and diabetes is not in sight.[63] Although excellent information is available,[64,65] there is no comprehensive, population-wide plan being implemented with any evidenced-based hope of reversing the rise in prevalence for either condition.[58,63]

Prevalence of risk factors is high

The current cardiovascular risk burden is oppressively high. According to recent NHANES data, about half of American adults have one or more of the three major risk factors: dyslipidemia, hypertension, or diabetes.[53] Approximately 13% have two of these risk factors, and about 3% have all three. The National Center for Health Statistics also estimates that 15% of adults have one of more of the three risk factors but remain undiagnosed and hence untreated. The 2010 Update on Heart Disease and Stroke Statistics[1] reported the following prevalence rates from various sources: 34% hypertension, 33% obesity, 32% pediatric obesity or overweight, 29% prediabetes, 8% undiagnosed diabetes, 34% metabolic syndrome, 21.2% tobacco use, and 59% abstaining from any vigorous activity. Other reports, a short interval later, indicate a higher incidence of hypertension, 36% prediabetes, and 27% undiagnosed diabetes, and 11.2% of adults with both prehypertension and prediabetes.[2] In 2009, the diabetes population was predicted to double or triple within 25 years.[60] During the same period, a review of surveys estimated that among Americans ≥30 years, 13.7% of men and 11.9% of women had diagnosed diabetes, and about one-third of them had not yet been diagnosed. The most recent data from the CDC[66] amended these figures, reporting a rise in prevalence of prediabetes to 35% in adults older than 20 years, to 50% in those over 65 years of age. The strain on the healthcare system resulting from both obesity[67] and diabetes is remarkably high.[60,68] Since the surveys incorporate older information, self-reporting, and imperfect criteria in some instances, actual prevalences may be higher for all risk factors. For instance, the quoted 34% prevalence of metabolic syndrome is based upon NHANES 2003–2006 figures, and is now significantly higher in the USA, reaching 53% in some subpopulations. Hence in the 2011 Update on Heart

Disease and Stroke Statistics,[69] the members of the writing group noted that "prevalence and control of traditional risk factors remains an issue …" The prevalence of obesity may be rising ≈1.4% every 2 years in America, with the current prevalence of visceral obesity at ≈53%.[70]

The magnitude of the burden of risk factors may in fact be underestimated. Recently 1,933 middle-aged subjects in the community-based Heart Strategies Concentrating on Risk Evaluation (Heart SCORE) study were evaluated for the seven characteristics – behaviors and factors – of ideal cardiovascular health as defined by the AHA.[71] Only one participant (0.1%) met all of them, and fewer than 10% of met ≥ five components of ideal cardiovascular health. Thirty-nine subjects (2.0%) had all four components of ideal health behaviors, while 27 (1.4%) had all three components of ideal health factors (Table 1). About 81% of their cohort was overweight or obese, possibly due to a high proportion of blacks (44%), and low prevalence of cardiovascular health was noted in all subgroups: ethnicity, gender, education, and income. Blacks had 82% lower odds of having ≥ five components of ideal cardiovascular health (odds ratio 0.18, 95% confidence interval [CI]: 0.10 to 0.34; $P < 0.001$). These numbers offer a telling summary, and suggest that when risk factors are carefully evaluated, a truer, even more gruesome index of the present risk burden emerges. Indeed, in this study one limitation was the possibility that the level of cardiovascular risk in the general population might even be higher, because volunteer participants had a relatively low prevalence of tobacco use and a high educational level.

Epidemiologists identify three phenomena now accelerating cardiovascular risk: obesity, diabetes, and the progressive aging of the population.[72–76] The first two, obesity and diabetes, including metabolic syndrome, respond to primordial, primary, and secondary prevention. The third, a higher proportion of the elderly within the population, is of course, untreatable. Reversal of traditional risk factors in elders is, however, beneficial and presents therapeutic opportunities.

The level of cardiovascular risk in children and young adults is also of major concern,[77,78] with one-third of this population overweight or obese. As a result of an epidemic of childhood obesity and the rising appearance of diabetes type 2 in the pediatric age group, the number of risk factors now found in children is alarming. Physical activity is below recommended levels in 17% of adolescents, and 20% of this population has at least one abnormal lipid value.[79] Cardiovascular risk, even in the pediatric age group, forms a continuum that has been carefully tracked over the human lifetime, with dominant and close associations between risk factors, CHD risk, and poor outcomes along the way.[80,81]

Screening and control of cardiovascular risk

Despite the high burden of cardiovascular risk, screening receives a disproportionately small amount of attention and support. Given the comparative death rates and numbers succumbing to cardiovascular disease (CVD), cancer, and HIV, the screening frequencies and filters for asymptomatic CVD (BP, ambulatory monitoring, lipid profiles, advanced lipid testing, others) are much less favorable than for cancer (with less than 10% of the funding, based upon breast examinations and colorectal screening data) and HIV than for asymptomatic CVD.[82] In addition, support and enthusiasm for primary prevention, eg, an initial myocardial infarction (MI), is woefully behind that for secondary prevention (recurrent MIs), although the benefits may be greater over an enlarged population base and longer horizon for the former.

In addition, there is ongoing concern that control of risk factors, although progressively improving, still remains far from evidence-based targets.[11] A review of NHANES data from 2005 to 2008 recently quoted a prevalence of hypertension in American of ≈31%, about 70% receiving treatment and a control rate of 46%.[83] An accompanying report, also from the CDC for the same period,[84] estimated 33.5% of adults had elevations in LDL-C, only 48% received treatment, and 33.2% were controlled. Overall, well over half of the population with risk factors does not have them under control, and ≤10% with multiple risk factors have them within target ranges.

Poor adherence is itself a major "risk factor" of substantial complexity and underrated significance.[85–88] About one-quarter of all new prescriptions are not filled,[89] and fewer than half of patients may eventually be taking the drug prescribed.[90–92] Therefore, when one discounts the patients who are undiagnosed, undertreated, considers adherence shortfalls, and significant residual risk, discussed further below, it becomes evident that current prevention effectively reduces a far smaller portion of total cardiovascular risk than is customarily believed.

Global risk burden is high

High burdens of cardiovascular risk exist world-wide, as reported by the Institute of Medicine,[5] World Heart Federation, and in the EuroAspire studies.[93] Pediatric obesity has also become a global menace.[94] Similarly, the worldwide prevalence of diabetes is an imposing problem,

with a staggering 69% rise in numbers of affected adults in developing nations anticipated by 2030, over three times greater than in developed countries,[95] which will tax health care systems everywhere.[96] All told, while effective prevention of diabetes is well-documented, new data creates uncertainty, implementation is fragmented, and some initiatives remain in conceptual suspension globally.[97]

In the 2011 Heart and Stroke Foundation Report on Canadians' Health, risk burden was considered high. The perceptions of self-reported behaviors were compared to the best estimate of actual prevalence of five general risk factors. They concluded that in four categories Canadians were in denial about their health behaviors.[59] As noted elsewhere, self-reporting of health habits is often inaccurate because positive behaviors are overreported, and negative habits are underreported. In this instance even as reported, a disparity between perception and actual frequencies were identified (Table 3). A similar table based upon NHANES or EuroAspire data would show even greater discordance in the USA and EU. Of concern are the numbers of patients not asked about their use of tobacco or family history for heart disease, and in whom no weight or blood pressures were recorded by practitioners during visits. In an effort to improve cardiovascular risk factors, a web-based e-tool is available as a smart phone application, *My Heart&Stroke Health App*™, is downloadable from www.heartandstroke. ca/mobileapps, or the interactive evaluation is also offered at www.heartandstroke.ca/risk. The reader will notice the similarity to the American Heart Association's Life's Simple 7™, indicating an endorsement by the HSF of the power and necessity of primordial prevention.

Risk burden in developing nations

All of the above generally applies to poorer developing nations, which have been included in the epidemic of chronic disease that sweeps across the world. Traditionally noncommunicable disease (NCD) deaths have been overshadowed by those from communicable diseases (CD), and therefore NCDs have not been included in development goals in such countries.[98] There is no nation in which the prevalence of cardiovascular disease will not rise in the next decade; only in sub-Saharan Africa does the prevalence of CD exceed or equal that of NCD. NCD accounts for about 60% of all deaths globally, and cardiovascular disease is a major cause. The relative rise in world-wide incidence of CVD is basically due to lower fetal and neonatal mortality, greater use of tobacco, and increased urbanization, with attendant rises in fat and energy consumption, lower physical activity levels, and, according to INTERHEART data, greater psychological stress.[99] Currently, emphasizing CD prevention rather than NCD only widens disparities in cardiovascular care to the poor, who have a high risk burden that leaves them vulnerable.[100] Thus far, conventional ideas concerning risk factors and subsequent development of cardiovascular disease appear to apply to developing nations, but it is unclear whether techniques and goals are relevant. Especially with considerable doubt about how best to control risk factors in a familiar and stable environment, whether we are in fact exporting inapplicable intensive "solutions" for different cultures is currently being debated. In other countries, such as China, it is anticipated that the principles successfully employed in Western nations will also be productive.

Franco et al[101] also call attention to the global emergency faced by countries of low- and middle-income, given the high burden of cardiovascular risk, the dire need for primordial prevention, and the multiple potential sources of resistance that impede implementation. The NCD Alliance, with The World Heart Federation as a component of The NCD Alliance, is aggressively urging implementation of the WHO 2008–2013 Action Plan for the Global Strategy for the Prevention and Control of NCDs, as well as the Global Strategy on Diet, Physical Activity and Health, which set forth strategies for primordial prevention.

Table 3 Cardiovascular risk factors as reported in the 2011 Heart and Stroke Foundation Report[38]

Risk factor	Self-reported perception (% participation)	Actual prevalence (%, estimated)	Not assessed by health care provider (%)	Impact upon life expectancy (years)
Smoking	23	20	37	−13.9
Obesity (age 18 or over)	18	24	Weight: 40% Waist measure: 67%	−4.0
Physically inactive in leisure time	31	48	44	−3.6
High blood pressure	17	19	18	−2.4
Vegetable and fruit intake <5+/day	39	54	52	−1.3

Data from the Heart and Stroke Foundation (HSF) poll of 2000 Canadians performed in December 2010, self-reported from the 2009 Canadian Community Health Survey, or from the 2007–2009 Canadian Health Measures Study.

Coronary heart disease begins in childhood and progresses throughout life

Primordial, primary, and secondary prevention are underpinned by convincing evidence that atherosclerosis begins in infancy,[102] has an incubation period of decades, and progresses throughout an individual's lifetime. At the same time, evidence is also accumulating that risk factors, such as obesity, have prenatal beginnings.[69]

The pathology of early stages of atherosclerosis in children and adolescents is a function of the same traditional risk factors that affect adults. Worsening of risk factors accelerates the disease, but their improvement slows or is even capable of reversing the process. The longer the exposure to, and the greater the intensity of, the risk factors involved, the higher the atherosclerotic burden will become.[103,104]

Epidemiological, pathological,[105,106] and risk factor data[79,107,108] confirm that the atherogenic process already incubates during childhood, and can even be detected in utero.[109] Fatty streaks, a common early manifestation of atherosclerosis and well-developed in many young adults, are present in 37% of asymptomatic, otherwise healthy organ donors from ages 20–29.[110] These findings are consistent with reports of significant coronary atherosclerosis in the majority of young soldiers who died on the battlefield.[111,112]

The Bogalusa Heart Study (BHS), directed by Dr Gerald S Berenson for the past 39 years, has clearly established the significance risk factors have in youth, now well described in about 1000 publications and four books.[78,80,113–117] Observations from the BHS show that the major etiologies of adult heart disease and atherosclerosis: hypertension, dyslipidemia, and obesity, begin in childhood, with anatomic changes evident by 5–8 years of age. Autopsy studies demonstrate lesions that correlate with risk factors[116] One of the most striking of the findings in the Bogalusa study, in addition to the early presence or progression of childhood risk factors, was their tracking into adulthood.[118] A recent contribution is a retrospective cohort study of adults 19–39 years of age who were followed for an average of 17 years since childhood.[115] Adverse levels of glucose homeostasis variables in childhood persisted into adulthood but also predicted adult pre-diabetes and diabetes, and correlated with cardiometabolic risk factors. In this regard, a significant relationship between excess visceral fat, dyslipidemia, hypertension, and elevations in CRP levels has also been established in children and adolescents.[119–121]

Magnussen et al[122] studied changes in adiposity (BMI, waist circumference, skinfold thickness), fitness (bicycle testing), plasma lipids (TC, LDL-C, HDL-C, TG), smoking and socioeconomic status (parental education level) in 539 young Australians in the Childhood Determinants of Adult Health Study. Baseline measurements were made in 1985 when participants were 9, 12, and 15 years old, and again between 2004 and 2006. Among those with hypertriglyceridemia in youth, 79% of males and 97% of females had normal values ~20 years later. The majority of those with elevated levels of HDL-C at follow-up had normal levels at baseline. Both TC and LDL-C tended to be more constant, and most youngsters with elevations at baseline had them at follow-up, later in life. When participants had adverse lipid profiles at baseline, if they also gained weight, or continued to smoke during the interval, at follow-up they were more likely to have dyslipidemia as well. Similarly, those without adverse lipid profiles at baseline were significantly more likely to have dyslipidemia later if they gained weight or continued to smoke in the interim. Last, those who had normal lipid profiles at baseline, but who developed higher risk at follow-up had greater gains in weight, reduced fitness, and failed to rise socioeconomically. Also of note was the association of long-term aerobic exercise training and upward social mobility from youth to adulthood, with higher HDL-C levels. The data suggested that, whether dyslipidemia was present or not in youth, risk factor modification significantly impacted risk when those individuals became adults some 20 years later.

The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) studied 2,876 persons 15–34 years of age who died of external causes, and found a strong concordance between coronary and aortic atherosclerosis and risk factors.[123–126] The early PDAY score of modifiable risk factors and its variation predict risk in youth and may be useful in identifying high risk individuals.

Recent imaging studies reflect the same pathophysiology. In the Coronary Artery Risk Development in Young Adults (CARDIA) study[81] of 3,258 individuals ages 18–30, the 87% with nonoptimal lipids were about 5.5-fold more likely to have coronary artery calcium deposits 20 years later, compared with participants with the lowest lipid values. Coronary calcium prevalence was 8% in young adults with optimal LDL-C levels (<70 mg/dL, or <1.81 mmol/L), but 44% in those with LDL-C cholesterol levels of ≥4.14 mmol/L (≥160 mg/dL). HDL cholesterol was also predictive. Hence, the CARDIA trial demonstrated that nonoptimal levels of LDL-C and HDL-C during young adulthood are independently associated with CHD 2 decades later.

The Cardiovascular Risk in Young Finns study[127] sought to determine whether childhood risk factors were

associated with a 6-year change in carotid intima-media thickness (CIMT) in young adulthood independent of the current risk factors. In 1,809 subjects who were followed for 27 years from baseline (in 1980, age 3–18 years), CIMT was measured both in 2001 and 2007. Childhood risk factors assessed included LDL-C, HDL-C, BP, obesity, diabetes, smoking, physical activity, and frequency of fruit consumption. In participants with zero, one, two, and ≥ three risk factors, CIMT increased during 6 years by 35, 46, 49, and 61 µm ($P = 0.0001$). This relationship remained significant after adjustment for adulthood risk. Of the individual childhood variables, physical inactivity and infrequent fruit consumption were associated with accelerated CIMT progression after adjusting for the adult risk factors. The associations of childhood lipid values and BMI with CIMT progression became nonsignificant when adjusted for current (adulthood) risk factor levels. A composite childhood risk factor score was also associated with CIMT progression and this score remained significant in adulthood after adjustment. In those risk factors with greater relative importance of adult values – HDL/LDL ratio and obesity – correction of adverse childhood factors in adulthood appeared to attenuate the ill effects of childhood burdens. The data therefore suggest that interventions to improve lipid and weight abnormalities between youth and adulthood would be productive.

Data from The Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (I3C) Consortium were combined in order to investigate the age at which risk factors influenced CIMT later in adulthood.[128] All together, 4,380 participants had TC, BP, BMI, TG measured from age 3–18 years, and CIMT was performed in adulthood, ages 20–45 years, mean follow-up 22.4 years. The number of childhood risk factors was predictive of higher CIMT when measured at ages 9, 12, 15, and 18 years, whereas associations with risk factors measured at 3 and 6 years were not significant. The greater the number of risk factors, the higher was the probability of a raised CIMT. A 9-year-old obese child with two additional risk factors would have double the risk of a CIMT in the top decile of the adult distribution, as compared with a child without cardiovascular risk factors.[129] The accompanying editorial noted that i) these data underscore the need to begin population-wide risk reduction in early youth, which is applicable to whites and blacks world-wide; ii) screening is meaningful from age 9 years onward; iii) current data indicate the absence of risk

factors in children is associated with a low likelihood of atherosclerosis; iv) screening for dyslipidemia, BP, and BMI in children is supported; but v) how to select those children for aggressive risk reduction remains unknown. Details about treatment of pediatric dyslipidemia are discussed in recent reviews.[130–137]

These studies are consistent with a model in which atherosclerotic lesions, initially in the form of fatty streaks, advance seamlessly over decades to more mature, fibrous plaques found later in life. The disease progresses, at different locations with variable rates, through adulthood[110–114,123,138,139] Intracoronary ultrasound studies in donor hearts demonstrates coronary artery plaques ≥0.5 mm in 17% of hearts in 13–19 year olds, which rises to 60% in 30–39 year olds.[110] The speed of progression depends not only upon the time of appearance of the risk factor, but also strongly depends upon the number of risk factors present. By the time lesions are identified, or symptoms appear, the disease is diffuse, elevations in systemic biomarkers may be present, and pathology has been in progress for years. Although a significant portion of the total duration of the disease precedes the diagnosis, the accelerated rise in risk – and events – may be skewed toward later years. This long asymptomatic period, traditionally ignored, needs greater attention and simultaneously provides untapped opportunity.

Since lifestyles and behaviors affecting cardiovascular risk are learned early in life, health education should be emphasized at that time.[78] Epidemiologists, preventive and pediatric cardiologists, and pathologists all agree that up to 90% of heart disease can effectively be prevented, and promotion of healthy lifestyles, nutrition and adequate exercise should begin in childhood. Moreover, while risk factors are already significant in young adults (59%) and LDL-C elevations are not uncommon, screening remains inadequate.[140] Among 20,266 fifth-grade children from the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project (796), 71.4% of children met the National Cholesterol Education Program (NCEP) guidelines for cholesterol screening on the basis of positive family history. Of those, 8.3% had an LDL-C ≥130 mg/dL; 1.2% of them were eligible for treatment with an LDL-C ≥160 mg/dL. Of the 28.6% who did not have a positive family history, ie, did not meet NCEP guidelines, 9.5% had an LDL-C ≥130 mg/dL, and 1.7% with LDL-C ≥160 mg/dL warranted treatment. Therefore, many children with dyslipidemia are being overlooked, since family history is not an effective indicator for screening. Weight was not a variable in the study.

While the composition of the "ideal diet" for cardiovascular protection continues to be debated,[63] it is not the uncertainty of dietary efficacy upon lipid levels to lower risk, nor lack of knowledge about other risk factors upon cardiovascular outcomes, but rather ineffective implementation that impedes meaningful progress. Unfortunately, individual-, school-, and community-based programs thus far have had mixed results for a number of reasons.[125,141] The rise in pediatric obesity is of concern to pediatricians,[142–144] and endocrinologists.[145] Despite the evidence linking early presence of risk factors and adult risk, confirmatory data from other studies, and recent emphasis on primordial prevention, relative inaction on the part of public health authorities continues.[117] Dr Berenson, with a half-century of experience, aptly summarizes the present status of preventive cardiology as a "hard sell", despite overwhelming acceptance and vocal support.

Global cardiovascular risk scoring for stratification

For primary prevention patients, guidelines recommend, and many physicians use, the classic Framingham Risk Score (FRS) to objectively estimate the absolute risk of a coronary event (CHD) during a period of 10 years[146–149] Inputs of age, gender, total cholesterol, tobacco use, HDL-C, TC, systolic blood pressure, and treatment status are entered into multivariable equations. The combination of risk factors generates a risk estimate for fatal and non-fatal CHD events, and subjects are classified into high-risk ($\geq$20% risk), intermediate-risk (10%–20%), and low-risk (<10%) categories. A number of global risk score alternatives to FRS exist based upon different cohorts – SCORE,[150] QRISK[151] ASSIGN,[152] the 2001 ATP-III Risk Estimator (FRS-based)[153,154] and PROCAM[155] – as well as the Reynolds Risk Score incorporating CRP for women[156] and for men[157] (Table 4). Risk scoring is a considerable improvement over personal physician judgment, and has been used for stratification and to guide evidence-based treatment.[158–161] Each scoring system is most accurate when applied in the population used for its development. Calibration – the extent of agreement between what is observed and predicted – depends upon prevalence of risk factors and coronary event rates in given populations. For American Indians and Americans of Asian-, Chinese- and Hispanic-descent, the FRS overestimates risk, which may be corrected with recalibration. FRS scores are clinically validated,[154] globally accepted, and have withstood the test of time. Dent[162] suggested that the prevalence of CHD in Framingham has been reduced by improvement in risk factors, particularly smoking, and this change in population characteristics accounts for inaccuracies when using FRS tools. He also believes that since the original cohort was Caucasian and socioeconomically advantaged, the FRS may be limited when applied to ethnically diverse groups.[162] In a variety of populations in North America, average FRS 10-year predictability of CHD is approximately 65%–70%.[154] The FRS does not include a family history of premature cardiac events, an independent and powerful risk factor for CHD.[163–168] To enhance features and utility, another version of the FRS was developed to predict 10-year global cardiovascular risk and specific events of CVD: coronary, cerebrovascular, and peripheral arterial disease and heart failure.[169] Unfortunately, there is suboptimal use of scoring systems providing estimates of absolute 10-year risk, with only 17%–47% of practitioners performing such assessments.[170–173] An informal survey suggests actual use among cardiologists and internists may even be lower.[174] A recent preliminary report from the PARADIGM registry indicated that as many as 65.7% of high-risk patients in Canada were being misclassified, with about 34% of primary-care physicians using the FRS, 28.5% relying upon clinical judgment, while others are misapplying CRP recommendations based upon JUPITER findings.[175]

While the FRS represents a remarkable advance in primary prevention, is well-known, well-studied, and is in widespread use, some shortcomings have been identified, and there are no randomized controlled trials showing that its use improves outcomes.[162,176,177] In some European regions and in low-risk populations the FRS may overestimate risk by a factor of 2.87, but underestimate it by a factor of 0.43 in high-risk populations.[178] In women who sustained their first myocardial infarction, 95% had FRS scores in the low risk category, with the remaining 5% in the intermediate category.[179] Using the NCEP-ATP III/Framingham risk estimator,[153] 17% of women in this cohort were ineligible for statins. According to the Framingham Heart Study, 39% of asymptomatic women over age 50 will eventually suffer a cardiovascular event, but the Third National Health and Nutrition Examination Survey[180] indicates that just 0.9% of asymptomatic women will be in the high-risk FRS category.[27] Using the ATP III tool, for most combinations of risk factors, the majority of nonsmoking men <45 years of age and nearly all women <65 years of age will have 10-year risks <10%, leaving many young individuals with sizeable risk burdens that remain untreated.[181] FRS may predict satisfactorily in 33% of women, and in 85% of men, for a combined prediction rate of 63%.[182] The lowest quoted is about 11%.[183] The c-statistic, a number which reflects how a model discriminates

Table 4 Currently available cardiovascular risk scoring models

Study	Input variables	End point	Region of origin, age, gender	Limitations and comments	Website URL
Framingham Risk Score[146–149]	Age, sex, BP, smoking, use of HTN meds, TC, HDL-C	All CHD	US, Caucasian volunteers in Mass, M, W, 30–62+ years	Well-studied, classical, user-friendly scoring system in widespread use. Sample size of ≈8500. Poor in Hispanic M, Native-American W, Japanese-American M, in presence of DM2, LVH, severe HTN. Underprediction of 0.43 in high-risk, but overprediction of 2.87 in low-risk populations. Misclassification may result in ineligibility of low risk individuals who may benefit from statins. Recommended by NICE until February, 2010, thereafter defaulted to local preference. See text for details.	http://www.framinghamheartstudy.org/risk/coronary.html
NCEP-ATP III (Framingham)[153,154]	Age, sex, sBP, smoking, use of HTN meds, TC, HDL-C	CHD death, nonfatal MI	Universally applicable US, relies upon FRS	Risk algorithm used (2004): High risk: ≥ two risk factors, FRS > 20% or with CHD, DM, PAD, aortic aneurysm, significant or symptomatic carotid artery disease; Moderately high risk: ≥ two risk factors and FRS 10%–20%; Moderate risk: ≥ two risk factors FRS < 10%; Low risk: zero to one risk factor. Misclassification in low risk category may result in denial of statins to persons who might benefit. See text for details. New ATP IV guidelines are scheduled for release in Fall, 2011.	http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm Calculator: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof ATP IV: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp4/index.htm Compare Joint British Societies Risk 2009: http://www.bhsoc.org/Cardiovascular_Risk_Prediction_Chart.stm and NICE remarks: http://www.nice.org.uk/guidance/CG67
Framingham global CVD[169]	Age, sex, sBP, smoking, use of HTN meds, TC, HDL-C, DM	CVD death, stroke, HF, claudication, All CHD	US, Caucasian, M, W, 30–74 years	Caucasian population. Version of FRS to include angina, stroke, PAD, and HF.	http://www.framinghamheartstudy.org/risk/gencardio.html
SCORE[150]	Age, sex, smoking, use of HTN meds, TC or TC/HDL, low and high CVD risk	CVD death only	EU, M, W, 40–65 years	Large sample size of ≈205,000 pooled from eleven European countries estimating 10-year risk of initial fatal event only. Regional risk system. Used in European Society of Cardiology guidelines.	http://www.escardio.org/communities/EACPR/toolbox/health-professionals/Pages/SCORE-Risk-Charts.aspx for EU high and low risk regions. Individual countries available at www.HeartScore.org
ASSIGN[152]	Age, sex, sBP, TC, HDL-C, FH, social deprivation	CVD death, CHD admission, CABG, PCI	Scotland, M, W, 30–74 years	Based upon a random Scottish sample size of ≈13,300. May overestimate risk. Recommended by the Scottish Intercollegiate Guidelines Network.	http://www.assign-score.com/
QRISK[151]	Age, sex, sBP, smoking, use of HTN meds, TC/HDL, FH, BMI, social deprivation	CHD, MI, stroke, TIA	UK, M, W, 35–74 years	Based upon a sample size of 2.29 million (QRISK2). Validated in same UK population used for derivation. Data from general practice registers in UK; not random, but able to be updated continuously. Recommended by NICE guidelines on lipid modification. High potential for UK method of choice.[162]	http://www.qrisk.org/and http://qintervention.org/

PROCAM[155]	Age, sex, sBP, smoking, LDL-C, HDL-C, DM	CHD death, nonfatal MI	EU industrial employees, M, W, 20–75 years	Based upon a sample size of ≈30,000 volunteers. Two separate scores calculate major coronary events and cerebral ischemic events. Recommended by the International Task Force for Prevention of Coronary Disease guidelines.	http://www.chd-taskforce.com/pdf/sk_procam_07e.pdf and http://www.assmann-stiftung,de/en/procam/procam-risk-scores/procam-health-check/
Reynolds, Women[156]	Age, sex, sBP, smoking, TC, HDL-C, CRP, FH, HbAlc if diabetic	CVD death, MI, stroke, revascularization	US, W, 45–80 years	Sample of ≈25,500 predominantly Caucasian W, upper socioeconomic health service employees. Volunteer, self-reported BP, BMI, FH. Data from the Women's Health Study. Compared to FRS, reclassified 5.8% of women, half to lower risk, half to higher. Lack of external validation; use of non-population based cohort to derive risk estimates.[189] Included in the Canadian Cardiovascular Society Guidelines as an alternative.[190]	http://www.reynoldsriskscore.org/
Reynolds, Men[157]	Age, sex, sBP, smoking, TC, HDL-C, CRP, FH, HbAlc if diabetic	CVD death, MI, stroke, revascularization	US, M, 45–80 years	Sample size of ≈11,000 predominantly Caucasian M, upper socioeconomic physicians. Volunteer, self-reported BP, BMI, FH. Data from the Physician's Health Study II.	http://www.reynoldsriskscore.org/

Notes: [a]World Health Organization/International Society of Hypertension (WHO/ISH) risk charts excluding lipid values are not shown; intended for countries with limited access to medical facilities, they are available at http://www.who.int/cardiovascular_diseases/guidelines/Pocket_GL_information/en/index.html. Other risk scores also have predictive potential, such as developed by the Consortium for Southeastern Hypertension Control in COSEHC-I I[191] with the advantage of data collection directly from electronic medical records.

Abbreviations: All CHD, CHD death; MI, unstable and stable angina; ASSIGN, Assessing Cardiovascular Risk to Scottish Intercollegiate Guidelines Network/SIGN to Assign Preventative Treatment; BMI, Body mass index; BP, Blood pressure; CABG, Coronary artery bypass graft; CHD, Coronary heart disease; CVD, Cardiovascular disease; CRP, C-reactive protein; DM2, Diabetes type 2; FH, Family history; FRS, Framingham risk score; HbAlc, glycosylated hemoglobin; HDL, High-density lipoprotein; HF, Heart failure; HTN, Hypertension; LDL, low-density lipoprotein; LH, Left ventricular hypertrophy; M, Men; Meds, medications; MI, Myocardial infarction; NICE, National Institute for Health and Clinical Excellence, UK; PAD, Peripheral artery disease; PCI, Percutaneous coronary intervention; PROCAM, Prospective Cardiovascular Münster; QRISK, QRESEARCH Cardiovascular Risk Algorithm; SBP, Systolic blood pressure; SCORE, European Systematic COronary Risk Evaluation; TC, Total cholesterol; TIA, Transient ischemic attack; W, Women.

risk for future events, is 0.7–0.8 for the FRS,[184] moderately good – a random coin flip is 0.5. Since CHD develops over decades, a 10-year horizon is insufficient to identify a significant group of people with relatively low risk at the time of scoring,[27,185] particularly young men.[181,186] In one study, about 45% of enrollees between 32 and 47 years of age had a low 10-year predicted risk, but a predicted lifetime risk of ≥39%.[187] Guidelines for primary prevention in women,[188] and the NECP Adult Treatment Panel III[153] have endorsed the use of lifetime risk in younger adults.

According to data using coronary CT angiography, about two-thirds of women and one-third of men with substantial coronary disease may be missed when the FRS misclassifies them as low risk,[192–194] because the initial physician is dissuaded from further screening.[194] Over 75% of CHD events in men and over 90% of CHD events may be misclassified in women. In addition, more than 25% of patients who are being treated with statins may have no detectable plaque on such imaging.

The 2010 ACCF/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults[32] assigned a Class I, LOE B recommendation for global risk scoring, advising that all asymptomatic adults without a clinical history of CHD should have their risk assessed using this method.

Recent discussions about screening for asymptomatic CHD and merits of scoring systems have raised unresolved issues beyond the scope of this review. For instance, how valid are claims of improved prediction beyond the FRS? One analysis showed that many such studies had limitations in design, analysis, or reporting that made improved predictive ability doubtful.[195] It should be noted that the Reynolds Risk Score,[156] which uses CRP levels and family history, and for which required metrics of adequate discrimination, calibration, internal validation, and reclassification have been satisfied, was not one of these. Another question is whether use of a risk-estimation system helps in risk factor reduction, as compared with graded treatment of each risk factor to guideline thresholds.[196–197] Should asymptomatic patients be screened for atherosclerosis at all, since there is little evidence clinical outcomes improve by doing so, but instead simply administer a polypill to adults of a certain age or dispense free statins in fast-food restaurants? One recent commentary concluded it is worthwhile to screen.[198] The accompanying editorial[199] observed that cardiovascular screening tests should be proven to prevent clinical disease, and that ability to predict or reclassify risk is secondary. One valid technique, they continued, is using the screen to

identify subjects thought to be at high risk, and randomize them to treatment or control,[200] as was done in the JUPITER trial.[199] Papers that appeared before JUPITER was published, and the subsequent analyses that followed, mentioned insufficient improvement in reclassification when CRP was added to scoring systems.[201,202] Results of large randomized clinical trials, such as JUPITER, provide strong, direct evidence of efficacy. Several recent discussions concerning merits of nontraditional risk factors are based upon statistical parameters.[203] In the clinic, practical reasons to use biomarkers are a) to refine a clinical decision that leads to an evidence-based change in therapy leading to improved quality of life, morbidity, or mortality, and/or b) to motivate a patient to understand, partner, and make lifestyle changes or adhere to drug or device therapies.

Use of multiple biomarkers to refine prediction of cardiovascular events has met with variable success.[204–209] Outcomes depend upon the markers selected, and is also a function of the population studied, particularly age, and the stage of the disease process. Recently multivariable regression was used in two middle-aged European populations totalling 10,466 participants, adding a 30-biomarker score which included N-terminal pro-brain natriuretic peptide, C-reactive protein, and sensitive troponin I to a conventional risk model.[208] A rise in 10-year risk estimation for cardiovascular events and significant improvement in reclassification was reported.

10-year risk vs lifetime risk

For the reasons discussed above, when risk scores are used to guide treatment, a considerable number of asymptomatic, low-risk individuals who may benefit from statin drug therapy over a period of time may not qualify. The current evaluation algorithm consists of dividing individuals without clinical heart disease into low-, intermediate-, and high-risk categories. Those with 10-year risks over 20% are begun on statin therapy after evaluation; intermediate risk individuals −10% to 20% – are given drugs for risk reduction and/or further noninvasive testing continues for additional stratification; low-risk persons are generally advised about diet and lifestyle modification. Within this paradigm of targeting higher-risk individuals, approaches to improve the yield have included a) lowering the target LDL-C level; b) lowering thresholds for treatment in each risk group; c) greater use of imaging to identify those individuals misclassified by absolute risk scoring; and d) replacing the 10-year risk horizon with lifetime risk.

The strengths of the relationships between individual risk factors with death vary not only with the risk factor,

but with the time frame and gender.[210] Lloyd-Jones and collaborators have studied the use of lifetime risk for CHD extensively.[27,52,165,168,185,210,211] These investigators noted that individuals younger than age 40–50 in a low-risk category with an initial FRS < 10% may have a surprisingly large risk burden and a high lifetime risk for CHD which may not be appreciated using current stratification techniques.[27,211] For example, the Coronary Artery Risk Development in Young Adults Study found that >90% of individuals 32–47 years of age had a predicted FRS risk of <10%, yet had a lifetime risk of ≥39%.[187] According to NHANES data from 2003–2006, about 56% of American adults have a low 10-year risk but a high lifetime risk, only 18% have high short-term predicted risk, and 26% have both low short-term and low lifetime predicted risk.[213] Moreover, just 8% of men and 14% of women enjoy optimal risk factors associated with a low lifetime risk for heart disease.[213] Some of the errors in risk estimation by the FRS arise from unpredictable changes that occur in risk factors over time, such as blood pressure and insulin resistance, which may increase relatively quickly with age.[214] Others arise from changes in the competing risk of death from causes other than CHD, such as tobacco use. Lifetime risks for CVD are comparable to those from extremely lethal diseases, and are generally higher than risks related to many cancers. At 50 years of age, however, the absence of traditional risk factors is associated with extremely low lifetime risk and significantly greater longevity.[27,168] People with favorable risk factors enjoyed much lower lifetime risks for CVD death than those with unfavorable profiles (zero vs ≥ three risk factors, 20.5% vs 35.2% for men; 6.7% vs 31.9% for women), along with longer survival (men, >35 vs 26 years; women, >35 vs 28 years).[168]

A striking example of the limitations of current risk assessment in relation to actual lifetime risk was provided by the work of Berry et al.[187] They stratified 2,988 persons ≤50 years of age from the Coronary Artery Risk Development in Young Adults (CARDIA) study[181,215–217] and 1,076 similar individuals from the Multi-Ethnic Study of Atherosclerosis (MESA)[217–219] into three groups: low 10-year (<10%) risk/low lifetime (<39%) risk; low 10-year/high lifetime risk (≥39%); and high 10-year (≥10%) risk or diagnosed diabetes mellitus (DM2). Among those with a low FRS, there were just as many participants with a high lifetime risk as a low lifetime risk, which implies that as many as half of individuals in this large low-risk group may fail to receive beneficial therapy.

In this investigation, coronary artery calcium (CAC) was also used to assess the degree of subclinical disease at baseline and after the study periods. In CARDIA, a CAC was performed at year 15 and year 20; in MESA, a CAC was performed at baseline, at about 22 months in 50% of participants, and at about 40 months in the remaining half. In addition, CIMT was performed in year 20 in the CARDIA study, and at baseline in MESA. In participants with a low 10-year risk, the vast majority in the study, individuals with a low lifetime risk compared with a high lifetime risk had significantly smaller dimensions of common and internal carotid intima-media thickness, as well as a lower prevalence and progression of coronary artery calcium.[187] The differences in CIMT dimensions in younger adults were believed to ultimately correspond to considerable increases in cardiovascular risk over the years. Hence, exposure of individuals to higher risk factor intensities over a substantial period of time leads to accumulation of atheromatous changes, eventually reaching the threshold that produces clinical events at older ages.[187,216] However, those individuals without risk factors at age 50 have a lifetime risk of CVD of approximately 5% over a generously extended lifespan.[27]

Consideration of lifetime risk is clearly important, not simply philosophically, but in treating patients in the real world. In view of these data, reports suggesting that statins are being overprescribed on the basis of 10-year risk estimations,[220] or even a single CAC study,[221] are of concern, and at the least, suggest further trials are needed. Not only in America, but globally, the facts indicate otherwise – that statins are underprescribed, and strikingly so, given the level of prevailing risk.[222] Moreover, if low CAC scores only provide a "warranty" for a period of 4–5 years,[223] retesting at such intervals to assess need for statins in patients who are likely to undergo additional diagnostic imaging could significantly raise the burden of radiation exposure, particularly if CAC screening widens.[224–226]

Nambi and Ballantyne,[227] editorializing on the broader significance of these findings in risk stratification, also observed that within classically-measured low-risk cohorts of the "healthy" population, there was a significant difference in observed risk over 14 years of follow-up in their own work,[228] and concluded that the evaluation of "low-risk" patients needs to be reassessed.

A new multi-level risk stratification proposal has been made using the FRS as the first tier, lifetime risk as the second filter, and CRP levels, with CAC and CMIT in a third tier to guide LDL-C-lowering therapy.[227] These are the major tools that are considered important for risk assessment Recent data reflecting improved long-term safety and cost-effectiveness

of statins, even at FRS risks ≈10%, are additional reasons favoring statin therapy when predicted risk is in the lower end of the spectrum.[76]

The data mentioned above are consistent with increasing awareness that the prevalence of ideal cardiovascular health in the population is low, and the greater number of cardiovascular events will ultimately rise among individuals who are not in a high-risk category.[2] The information presented also adds to the growing body of evidence underscoring the importance of not only preventing development of risk factors at the earliest opportunity, but also screening sooner, stratifying more efficiently, and using intensive therapies to reduce risk.

Early, aggressive treatment is the new imperative

Early detection of atherosclerotic disease and refinement of risk assessment has been accompanied by a recent sea change in the thinking about the timing and aggressiveness of treatment of risk factors, in both ostensibly healthy individuals who are not investigated further than "routine" LDL-C levels, and those with established CHD.[2,27,28,52,185,229–232] The regression line for major statin studies shows that LDL-C reduction produces benefits in a linear fashion approaching "physiological" levels (see section below). The Cholesterol Treatment Trialists study suggested outcome improvement in statin-treated patients with baseline LDL-C ≈80 mg/dL.[233] The evidence for aggressive LDL-C lowering for high risk patients has been recently discussed elsewhere.[234,235] Notably, Steinberg and coworkers[138] called attention to the urgent need for earlier intervention in reducing risk factors, especially LDL-C, adding to the consensus.

Due to the evolution of disease-reactive medical care, escalation of clinical assessment and treatment usually follows the finding of either abnormal biomarkers or symptoms. Waiting until this occurs in CHD, with its long incubation period, is a prescription for certain failure of "primary" care. By the time elevations in LDL-C or CRP occur, especially at levels mandating therapy using current guidelines, the disease is widespread, relatively advanced but still often inaccessible to customary techniques used for detection. Consequently, the improbability of intervening early enough has generated skepticism about whether prevention is ever "primary".[236] For instance, studies using intravascular ultrasound (IVUS)[237–242] and intracoronary optical coherence tomography[243,244] amply demonstrate plaque in various stages of evolution invisible to routine coronary angiography due to limitations in resolution and view.

Proprotein convertase subtilisin-like/kexin type 9 serine protease (*PCSK9*) is a gene encoding PCSK9, a protease expressed in the liver and intestine in adults. The liver releases PCSK9 into the circulation, concentrations of which correlate with BMI, triglyceride, TC, and LDL-C levels, as well as blood pressure, fasting blood glucose, and gamma-glutamyl transferase levels. The protease is a molecular chaperone, bindling to the epidermal growth factor-like domain A of the LDL receptor, redistributing the LDL receptor from the plasma membrane to an endosomal/lysosome pathway for degradation.[245] *PCSK9* thereby regulates LDL receptor levels on the cell surface, particularly in hepatocytes.[246] Individuals with *PCSK9* loss-of-function mutations have LDL-C levels about 28% lower than nonvariants.[247,248] About 3% of the population may have these variations. Such changes correspond to an 88% fall in risk for CHD events, nearly three times the reduction of a 5-year course of statins that reduces LDL-C comparably. On the other hand, gain-of-function mutations in *PCSK9* results in diminished net expression of LDL receptors, producing a clinical picture resembling familial hypercholesterolemia.[249,250] This experiment of nature suggests that favorable levels of LDL-C begun early, and maintained throughout life, are needed for optimum reduction in CVD events. Using the data from *PCSK9* studies, Steinberg[251] calculated that beginning statin therapy much earlier might double the yield and prevent 240,000 coronary events annually, based upon 2009 CHD mortality data.[1] By any account, benefits associated with the use of statins and other preventive therapies over a 3.7–5.0-year span of a study would only be a fraction of the potential if applied over the total incubation period of CHD, 40–60 years.

In view of the above, aggressive intervention, when indicated, should be offered at the soonest opportunity to prevent disease progression and future coronary events.[107,138,252,253] The longer lipid-lowering therapy continues, the greater the reduction in relative risk.[233] Risk factors in youth are growing concerns among pediatricians. The ACCF/AHA 2009 Performance Measures for Primary Prevention of Cardiovascular Disease in Adults[254] suggested that lifestyle measures begin at age 18.

Forrester[255] emphasizes the difference between proof and inference, the need to begin treatment according to the pathogenesis of atherosclerosis rather than initial clinical manifestation, choose a lower physiologic LDL-C target, and adopt a new practical, but more effective, mindset. In view of the above, using CRP as a guide to earlier treatment from randomized clinical trial data, rather than by estimates of added increments in risk factor prediction using scoring

systems, is pertinent and timely.[52,256] Rosuvastatin and atorvastatin in higher doses are the preferred agents for both LDL-C- and CRP-lowering ability.[257,258]

Statins in primary prevention

Measures used in primary prevention customarily include smoking cessation, diet modification, physical activity, weight management, correction of dyslipidemia (lowering LDL-C globally, targeting subfractions of LDL including Lp(a), lowering LDL-P or increasing the size of LDL particles, raising HDL-C globally, targeting subfractions of HDL, reduction of plasma triglycerides (TG) and other TG-rich atherogenic particles), reducing blood pressure, controlling diabetes and insulin resistance in related syndromes, use of aspirin, and treatment of comorbidities that commonly raise CHD risk, such as chronic kidney disease. The WHO MONICA project found that over half of non-fatal MIs in young people are attributable to smoking,[259] and risk returns to baseline about 5 years after cessation.[260] For each cigarette smoked daily, the risk of MI rises by 5.6%.[12] For every 38.7 mg/dL (1 mmol/L) fall in plasma LDL-C, there is a corresponding 21% reduction in cardiovascular events.[261] A drop in systolic blood pressure of 10 mmHg may result in a decrease of cardiovascular mortality of 20%–40%,[262] which may be enhanced by using ambulatory blood pressure monitoring.[263] A reduction in risk factors has contributed to the fall in the incidence of MI since 2000,[264] corresponding to a decrease in the prevalence of smoking from 23.1% to 19.7%, and a drop in the prevalence of hypercholesterolemia from 17.0% to 16.3%. A 1% change in absolute risk may affect ≈2.2 million adults.[265]

Effect of statins on plaque volume

The use of intravascular ultrasound (IVUS), with a greater sensitivity than coronary angiography, provides a direct and revealing method of assessing the effect of statin drugs upon coronary atheroma.[237–241,266,267] In recent trials, there was a strong linear relationship between LDL-C values and atheroma progression rate, with a critical reversal level of LDL-C at 70 mg/dL. While the effects of statins upon lesions are evident, the extent of atheroma regression varies (Table 5). In the ASTEROID study,[230,242,267] rosuvastatin 40 mg lowered LDL-C by 53% and raised HDL-C by about 15%, accompanied by a significant reduction in atheroma volume in both coronary arteries that were angiographically normal as well as those with visible obstructions. Extension of these data with the use of quantitative coronary angiography (QCA) suggested slowing of progression as well as regression of lesions in different segments of the coronary tree.[240] Improvement in luminal dimensions, as measured with QCA, correlated with risk of coronary events and mortality.[268,269] Changes in atheroma volume, stratified above or below a median change of −21.4% in CRP levels and −37.1% in LDL-C, was greatest in those with reductions in both LDL-C and CRP (−2 mm³), less when CRP fell but not LDL-C (−1 mm³), progressed when LDL-C fell but CRP was high (+2 mm³), and progressed the most when both LDL-C and CRP were high (+8 mm³).[230]

Serial computed tomography angiography (CTA) was performed in 32 older patients, 24 of whom took fluvastatin after the baseline CTA, with eight subjects who declined statin therapy serving as controls. After a median period of 12 months, plaque volumes were calculated in a 10 mm segment selected for comparison. Plaque volumes were significantly reduced in the statin-treated group.[276]

These data support a model in which atherosclerosis advances unpredictably in multiple sites at different rates. When LDL-C is lowered with statins, particularly rosuvastatin, the progression of the lesions may wane, some

Table 5 Recent statin regression trials using coronary IVUS

Investigators	Type	Statin used	Exam interval	Primary endpoint	Results (mean ± SD)
Petronio et al[270]	RCT	Simvastatin	12 months	Plaque volume	−2.5 ± 3.0 mm³/mm
		Control			1.0 ± 3.0 mm³/mm
Tani et al[271]	RCT	Pravastatin	6 months	% change in plaque volume	−14.4 ± 23%
		Control			1.1 ± 4.6%
ASTEROID[230,242]	Not RCT	Rosuvastatin	24 months	Change in PAV	−0.98 ± 3.15%
Takashima et al[272]	Not RCT	Pitavastatin	6 months	% change in plaque volume	−10.6 ± 9.4%
		Control			8.1 ± 14.0%
COSMOS[273]	Not RCT	Rosuvastatin	18 months	Change in PAV	−5.1 ± 14.1%
JAPAN-ACS[274]	RCT	Atorvastatin	8–12 months	% change in plaque volume	−18.1 ± 14.2%
		Pitavastatin			−16.9 ± 13.9%
Hirayama et al[275]	Not RCT	Atorvastatin	28 weeks	% change in plaque volume	−9.4 ± 10.3%
			80 weeks		−18.9 ± 14.1%

Abbreviations: RCT, randomized controlled trial; PAV, percent atheroma volume.

with complete regression. Whether these events are evident is also a function of the sensitivity of the technique used for assessment.[277] Even when LDL-C is lowered drastically, approaching "physiological" levels, however, some lesions may still progress in many patients.[278] This would include primary prevention patients, who may be so classified as a result of relatively insensitive techniques, but in whom the process is already under way. While unproven, preliminary evidence suggests that when CRP levels are elevated, especially in patients with metabolic syndrome, residual risk is likely to be high, a correlation may exist with CIMT, and the response to rosuvastatin may be greater.[279,280]

Statins recommended in guidelines

Several primary prevention guidelines from the USA, UK, and EU are available to assist clinicians, and the use of statins is typically recommended.[12,153,158–160,188,281–285] According to the last NCEP-ATP III recommendations for primary prevention, statins should be begun when LDL-C ≥190 mg/dL in individuals with low risk, is discretionary when LDL-C is 160–189 mg/dL, and is not advised for ostensibly healthy persons with LDL-C <160 unless there are ≥ two risk factors.[286] All are fairly high numbers, considering that 50 mg/dL might be "physiologic", and soon NCEP-ATP IV will announce modified targets. The ACCF/AHA/ACP 2009 Competence and Training Statement on primary prevention[287] succinctly reviews the essential role of lipid management, and advises that intensity of therapy match the individual risk for CAD in each patient. The overriding fact of life is that since the vast majority of people will not follow required lifestyle changes, patients with elevated cardiovascular risk will be treated with statins. Statin drugs have revolutionized the practice of cardiology over the last two decades, and there are no equals.

Analysis of statin use in primary prevention

There are seven systematic reviews examining the use of statins in primary prevention.[288–294] Mills et al[290] pooled results from 19 randomized trials to evaluate the effectiveness of statins in primary prevention. For 19 trials examining all-cause mortality, the relative risk (RR) was 0.93, and for 17 trials, using major cardiovascular events, the RR was 0.85. Overall, they concluded statins have a clear role in primary prevention of major events and mortality. Brugts and coworkers[291] included ten trials involving 70,388 people, 34% women and 23% with diagnosed diabetes, all with risk factors but without established cardiovascular disease. Statin therapy

lowered all-cause mortality (odds ratio [OR]: 0.88), major coronary events (OR: 0.70), and major cerebrovascular events (OR: 0.81). Mean follow-up time was 4.1 years. Since many trials did not consider death after a morbid cardiovascular event, the 12% risk reduction in mortality may have been an underestimate. Even though no clinical heart disease was identified, the pooled risk in the study population was high, and overall annual mortality was about 1.4%. Yet the relative risk reduction from statin use for primary prevention was comparable to that for secondary prevention.

A recent meta-analysis of the use of statins and all-cause mortality in high-risk primary prevention was performed by Ray et al.[292] Eleven randomized controlled trials involving 65,229 participants treated with statins for an average of 3.7 years were found to have no statistically significant improvement in all-cause mortality. In those treated for primary prevention, average LDL-C levels fell from 139 to 98 mg/dL (multiply by 0.0259 to convert to mmol/L). Compared to a mean placebo death rate of 11.4 per 1000 patient-years, there were only seven fewer deaths for every 10,000 patient-years of statin treatment.

The investigators emphasized the need to tease out patients with preexisting heart disease, because those patients would be the ones known to benefit from statin therapy. Although they were critical of other studies because of the short periods of study, the 3.7 year period of their meta-analysis was also relatively small. While the authors acknowledged statin efficacy in patients with diagnosed CHD, ie, for secondary prevention, they challenged statin use in low-risk patients when applying current prevention guidelines.[31,293,294] Because this study was a meta-analysis, there was considerable heterogeneity in patient risk and statin use, and some of the data used were old. In addition, the limitations of meta-analyses are well-known, but apply equally to the analyses that found statins do improve mortality in primary prevention.[290,291]

The reaction to this study was muted, with the consensus believing that in a primary prevention cohort, the period of statin treatment involved was insufficient to show more, and that a reduction in CHD mortality, combined with the long incubation period of atherosclerosis evidenced by results of longitudinal studies, justified treatment with statins. Waiting years for treatment in primary prevention would be an imprudent delay, according to most observers.

Bukkapatnam et al[295] focused their meta-analysis on women and included 6 studies, including JUPITER, totaling 21,963 moderately hyperlipidemic women given statins for primary prevention. These investigators found that

the summary risk ratio for any CHD event was 0.78 (95% CI: 0.64–0.96; $P = 0.02$), but there was no demonstrable reduction in all-cause mortality or CHD deaths. They attributed the better results reported in JUPITER, in part, to the stronger predictive power of CRP in women than in men. However, Bukkapatnam,[295] like Brugts and coworkers,[291] included data from the Primary Prevention of Cardiovascular Disease With Pravastatin in Japan (MEGA) study, conducted at 924 sites from 1994–2004.[296,297] This trial randomized 7,832 healthy men and women to pravastatin 10–20 mg with dietary modifications, or dietary modifications alone with a median follow-up of 5.3 years. MEGA found that statin therapy lowered CHD events by 33%, and relative risk for CVD events by 30%. Since the mean fall in LDL-C levels was just 11%, the statin produced an effect greater than would be expected from the reduction in LDL-C. While agreeing with the JUPITER trial discussed below, in that a statin was effective in lowering cardiovascular events in low-risk individuals without heart disease, some caveats are in order. At the time of the study, the prevalence of CHD in Japan was much less than in the countries in which JUPITER was conducted, and pravastatin in the doses used was considerably less potent than rosuvastatin 20 mg.

Taylor and coworkers[298] analyzed randomized controlled trials of statins in primary prevention with a minimum duration of 1 year, a follow-up of at least 6 months in adults, and also excluded ≤10% of participants with a history of CVD. Of the 14 trials included, 11 recruited patients with hyperlipidemia, diabetes, hypertension and microalbuminuria. Statins were associated with a 17% reduction in all-cause mortality (RR: 0.83, 95% CI: 0.73 to 0.95), lowering of combined fatal and non-fatal CVD endpoints (RR: 0.70, 95% CI: 0.61 to 0.79), with variation that was attributed to different populations, statins employed, and reporting (Table 6). The investigators concluded that no significant harm or change in patient quality of life was caused by statins, and they reported sizeable improvement in all-cause mortality, CHD, and stroke events, as well as number of revascularizations. According to their review, there was selective reporting of outcomes, failure to report adverse events, and inclusion of participants with diagnosed CVD. Despite the evident

Table 6 Outcome improvements with statin therapy in primary prevention found in the Cochrane review[298]

Outcome	Risk ratio (95% CI)
Total mortality	0.83 (0.73–0.95)
Fatal and nonfatal CHD events	0.72 (0.65–0.79)
Fatal and nonfatal stroke	0.78 (0.65–0.94)

positive benefit/adverse event ratio, they cautioned against use of statins in primary prevention patients thus: "below a 1% annual all-cause mortality risk or an annual CVD event rate of below 2% observed in the control groups in the trials considered here – [statin therapy] is not supported by the existing evidence". They further commented that there was insufficient demonstration of improvement in quality of life and cost-effectiveness associated with statin therapy.

Responses to these findings were immediate, strong, and largely opposed the authors' conclusions. The accompanying editorial[36] cited a number of concerns. A major one revolved around the limitations inherent in uniting the diverse published data. Baigent,[233] whose more complete work in the Cholesterol Treatment Trialists' Collaboration was not considered, vigorously challenged the conclusions, citing the significant benefits of statin therapy in relation to safety that the authors readily discussed, yet ignored. Other prominent researchers termed the study biased, inappropriately using data limitations that were irrelevant to the central issue. In addition, the conclusions were diametrically opposed to the growing evidence that statins are in fact underprescribed, rather than overprescribed,[222] and that less stringent criteria for the earlier use of statins would reduce total risk burden and subsequent events. Not only does the philosophy in the Cochrane review[298] disagree with current evidence-based guidelines, but also argues against the rationale behind many current programs and public health initiatives, including those advocated by WHO and disadvantaged countries, now exploring implementing the distribution of polypills. Lack of inclusion of all pertinent studies, the weights given to those considered, and subsequent interpretations were all criticized. Finally, it was said that adverse reactions, such as cognitive defects and depression, were given credence without adequate and critical examination of the evidence.

Sources of controversy regarding statin use in primary prevention

The American College of Cardiology, American Heart Association, National Cholesterol Education Program, NHLBI, and European Society of Cardiology incorporate statins in recommendations for both primary and secondary prevention. About 75% of patients who take statins do so for primary prevention. Presently the studies forming the basis for this prescribing are short, from 5–7 years' duration. The advice relies upon both scientific data and considered logical inference predicting that over a long period, cholesterol reduction will be reflected in improved mortality outcomes. Several researchers believe the use of

statins over an extended period of time has underestimated potential.[138,251,255,295,299,300]

As mentioned, patients with CHD already have widespread and advanced disease, but in general, the atherogenic process is fairly intense by the time a diagnosis is made. It is likely that the beneficial effects from statin therapy, particularly mortality, take a longer period of time to demonstrate during the earlier stages of the disease, ie, during primary rather than secondary prevention. The chief benefit of statins in primary prevention is reflected in lower rates of nonfatal MI. Because mortality is low in such patients, the sensible interpretation is that the therapy was not begun sufficiently early, was not potent enough, or not continued long enough for mortality benefits to become significant. Similarly, one would not ordinarily expect, for instance, a striking reduction in mortality after 3.7 years when treating hypertension or smoking for primary prevention. The implication of the Ray and Taylor studies is that, for a mortality reduction, one should consider denying statins to patients until risk is high (≥20% 10-year FRS score), or the initial coronary event or diagnosis is made. This view is consistent with the NICE approach,[283–285,301] but contrary to impressive data suggesting early and prolonged intervention is necessary. For the aforementioned reasons, the results of these meta-analyses will probably not be practice-changing. In summary, the absolute benefits of statins may be relatively small in a primary prevention population at low risk, and benefits are difficult to demonstrate short-term.

Given the economic constraints that exist in some countries, along with the political controversy surrounding health care delivery in the USA, the choice of medical services to be delivered now depends on factors other than science. Such issues may influence discussions in the academic literature. Most evidence indicates that population-based use of statins is in fact cost-effective, but this is a function of population characteristics, cut-offs used, and the statin involved.[302] The impact of generic atorvastatin was not considered in the Taylor study discussed above.

A large source of confusion about statin therapy concerns adverse reactions. There is a substantial amount of information circulating about side effects that is simply not evidence-based. Beliefs about the prevalence, severity, management, and threat of such reactions underpin reluctance to treat by practitioners and create unfounded fear in patients. Muscle aches and minor musculoskeletal discomfort are among the most common of human complaints, but when patients are taking statin drugs, a connection is assumed, commonly fueled by an inordinate number of inaccurate

discussions or anecdotes on the internet. Pertinent data do suggest that: a) side effects are "underreported" in published trials, in part an artifact of low myotoxicity due to strict screening and run-in periods; b) the incidence of side effects do not approach what is believed by some practitioners and consumers, eg, rates of ≈50% mentioned on the internet, compared to the actual ≈10%; c) life-threatening adverse reactions are extremely rare; d) most unwanted effects may be avoided and managed successfully; e) the incidence of intolerance and myotoxicity differs between statins; f) the benefits of statins far exceed those of adverse reactions, whereas other common drugs, such as aspirin, lack the same benefit/risk ratio in many settings.[15,303–306]

Statins and primary prevention in the elderly: a special population

Commenting upon a paper by Deedwania and coworkers in 2007, which reported that intensive statin therapy was not superior to a moderate approach in suppressing ischemia on monitor recordings in the elderly,[307] Gotto advised judicious application of statins in the elderly population pending further data,[308] which are now available.

Statins are underutilized in treating the elderly with cardiovascular risk, and a significant fraction of those individuals could benefit from statin therapy. Increasing age is a powerful risk factor, CHD is the most common cause of death in patients over 65 years, and over 80% of deaths due to cardiovascular disease occur in this population. The interaction of atypical presentations, multiple comorbidities, and polypharmacy may create uncertainty. Response to therapy is less predictable, while complications are more likely. Assigning causation, and prioritizing importance of pathophysiology from clinical and laboratory findings become difficult. When the benefit-to-risk ratio of treatment alternatives become unclear, caution prevails. With increasing age, relative risks of high LDL-C levels decline. Muscle and other side effects of statins often affect older patients' quality of life more than in the young.[309] All may contribute to the low attainment of evidence-based targets in this population.[310] Maroo et al[311] revisited the issue by reviewing four studies in the elderly, and concluded that statins provided benefit in high-risk older patients, even though they might be more susceptible to unfavorable interactions. A large meta-analysis of ten randomized trials in individuals with risk factors but without a diagnosis of heart disease showed substantial benefit to the elderly in both risk factor reduction and improved survival.[291] Wenger and Lewis,[312]

noting that a lack of awareness of potential benefits and perceived safety issues contribute to undertreatment, called for greater use of guideline-recommended LDL-C targets. Long et al[313] provide a recent authoritative discussion of details in individual trials.

Pletcher and Coxson[314] discussed the possibility that TC and non-LDL-C were stronger risk factors in the young than the old, with relative risks of 0.44/1-mmol/L fall in TC at ages 40–49 vs 0.72 at ages 60–69,[315] a relationship which they believed was also suggested in statin trials.[233] Pletcher et al[316] performed an analysis of age interaction of LDL-C and cardiovascular responses to statin therapy, and found that age may weaken statin effectiveness. Hayward,[317] however, disagreed, citing the absence of age-dependent variation in responses to statins in primary prevention in a survey by NICE.[283]

Glynn and collaborators[318] analyzed a subgroup of the JUPITER study of 5,695 persons over 70 years of age in the largest primary prevention statin study in this population. Compared to a cohort 50–69 years old, a greater proportion were women and hypertensive, with fewer smokers and overweight individuals. Reductions in LDL-C and CRP in the rosuvastatin-treated group were comparable to those in younger participants. The two groups combined demonstrated a 44% relative reduction in the primary end point of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, or confirmed death from cardiovascular causes. Even though their response to rosuvastatin was significant, 70% of the elders studied had an FRS > 10% and 65% were hypertensive. How much additional risk was conferred by elevated CRP levels was uncertain, since CRP levels rise with age.[319] A large number of the subjects would have qualified for statin therapy using conventional guidelines. Therefore it was not surprising that in the older patients, the nonhypertensive subset did not benefit from rosuvastatin therapy. Since the absolute reduction in risk was greater in the ≥70 year old group, the number needed to treat was 24, compared to 36 in the group aged 50–69 years. Overall, the data confirmed that in higher-risk elderly patients, rosuvastatin should not be withheld for fear of adverse effects.

Residual risk remains a source of concern

In preventive cardiology, residual risk commonly refers to risk remaining after statin therapy has achieved LDL-C targets. However, residual risk also exists when multiple risk factors are being treated simultaneously. To be sure, traditional or "major" risk factors account for the greater portion of risk, and the population-attributable risk for each one are known.[99] Non-lipid risk factors commonly coexist, and current practice guidelines recommend that all risk factors should be addressed for the best outcomes. Hence, a fuller definition of residual risk might be the vascular risk that persists after evidence-based targets are attained for dyslipidemia, hypertension, hyperglycemia, and inflammation.

Lipid-mediated residual risk during statin therapy

The average adult untreated LDL-C level in the USA is ≈130 mg/dL (3.4 mmol/L). Half of the individuals with "normal" levels ≈100 mg/dL (2.6 mmol/L) will have atherosclerosis by age 50.[320] In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT), aggressive lowering of lipids used only prevented ≈20% of cardiac events.[321] There is ≈30% relative risk reduction with aggressive statin therapy using current guidelines, resulting in about 0.5% lowering of major adverse cardiovascular events (MACE) per mg% reduction in LDL-C, amounting to a 24% MACE reduction per each 1 mmol/L fall in LDL-C.[234] This leaves a yearly ongoing incidence of MACE of ≈9% in such patients despite aggressive statin therapy.[233] PROVE-IT[322] and a dual target analysis of JUPITER[278] suggested that further reduction of LDL-C to ≈40 mg/dL may safely lower event rates even more. In the major well-known statin studies residual risk averages 65%–75%, and in studies aggressively lowering LDL-C to <100 mg/dL, residual risk persists. For this reason, simply reducing LDL-C to lower levels is of value, but residual risk is still significant. Use of more potent agents, such as rosuvastatin, with somewhat greater ability to raise HDL-C, may also be of benefit. For instance, in early statin studies using pravastatin, residual risk was ≈76%; use of rosuvastatin in the JUPITER trial was associated with a residual risk of 56%, certainly an impressive improvement.

Using intravascular ultrasound, Bayturan et al found that in about 20% of patients treated intensively down to a mean LDL-C of 58.4 mg/dL (1.5 mmol/L), plaque volume still increased.[278]

A portion of residual risk arises from atherogenic particles other than LDL-C, especially components of non-high-density lipoproteins (non-HDL). These include intermediate density lipoprotein, very low-density lipoprotein (VLDL), chylomicron and VLDL remnants, and lipoprotein (a). High triglyceride levels, low amounts of HDL-C, and defective HDL also contribute to risk. In the PROVE IT-TIMI

22 trial,[323] lower on-treatment CV risk was associated with TG <150 mg/dL. Cardiovascular event rates are higher when HDL-C is low in statin-treated patients,[233] while the additive risk of low HDL-C values is greater when LDL-C is low.[324,325] The EPIC (European Prospective Investigation Into Cancer and Nutrition)-Norfolk study[326] established that, independent of LDL-C levels, individual non-HDL-C ≥30 mg/dl higher than LDL-C predicted increased CHD risk, and triglyceride (TG) levels >150 mg/dL, or TC/HDL-C ratio >5 was associated with elevated risk for CHD. Carey et al[327] conducted a hospital-based, case-control study in patients at optimal LDL-C levels and also found strong and synergistic effects of high TG and low HDL-C levels upon CHD risk in patients with optimal rather than higher LDL-C, even <70 mg/dL. Specifically, there was a rise of ≈20% in risk associated with a 23 mg/dL increment in TG, and an increase in risk of ≈40% when HDL-C was 7.5 mg/dL lower. In patients who have achieved an LDL-C ≤70 mg/dL, Núñez-Cortés et al[328] estimated that an increase in HDL-C of 1 mg/dL would be expected to reduce the risk of subsequent MACE by ≈1.1%.

While most of the risk associated with obesity is mediated through hypertension, dyslipidemia, and hypertension, obesity itself is an independent risk factor. The pathogenetic events leading to raised cardiovascular risk in overweight and obesity are complex, heavily researched, remain ill-understood, but extend beyond metabolic, hormonal, and cytokine dysregulation[329–343] to include endothelial dysfunction, local pericardial fat accumulation,[341,342] liver involvement, and adrenergic disturbances.[315] Even when evidence-based targets are attained in all areas of traditional risk factors, residual risk persists. In diabetics, the risk is greater than is accounted for by the degree of separate risk factors. Inability to eliminate risk further by additional lowering of blood pressure,[345] glucose,[346] and through combination anti-lipid treatments[347,348] may be explained by a complex biochemical web producing risk in diabetes.[349] For these reasons, lifestyle modification and exercise remain fundamental cornerstones in the management of risk in these populations. In patients with diabetes and insulin-resistance syndromes, a "normal" baseline LDL-C sometimes creates reluctance to begin or intensify statin therapy, but in such patients with clearly elevated risk, benefits occur independently of initial LDL-C levels, and they should not be withheld. The sources of residual risk and management in patients with atherogenic dyslipidemia is further discussed by Hermans and Fruchart.[350]

High-density lipoprotein (HDL)

In general, a rise of 1 mg/dL in HDL-C is associated with a 3% lower CHD risk in women, and a 2% lower CHD risk in men.[351] Epidemiological studies associate low HDL-C levels with an increase in the rates of myocardial infarction (MI), stroke, and mortality. High HDL-C levels (≥60 mg/dL) are protective, whereas a low HDL-C level (≤40 mg/dL in men, ≤50 mg/dL in women) is an independent risk factor for future cardiovascular events; some guidelines advocate raising low HDL-C levels, especially in high-risk patients. In general, raising HDL-C levels is considered beneficial for much of the population.[241,352,353] NHANES 2003–2004[354] reported the mean HDL-C in the USA was 54.3 mg/dL, and was low in 27% of all NHANES participants, and in 35% of NHANES subjects with CVD. Hence prevalence of low HDL-C is common, affecting about one-third of the American population, with an HDL-C < 20 mg/dL found in ≈0.5% of men and ≈0.25% of women. HDL-C levels depend upon genetic and environmental factors, with lifestyle choices, including the use of alcohol and tobacco, among the reversible factors. As a result of the rise in the prevalence of obesity, diabetes, and the metabolic syndrome, the mean HDL-C in patients presenting with an acute coronary event has fallen during the past 10 years to 38 mg/dL.[355]

In 12,339 subjects without CHD at baseline in the ARIC study,[356] 10-year risk was lowest for those with LDL-C values in the lowest quintile (men, 95 mg/dL, women, 88 mg/dL) and lowest in the highest quintile for HDL-C (men, 62 mg/dL, women, 81 mg/dL). When adjusted for LDL-C, HDL-C, and TG, each 1 standard deviation rise in HDL-C, 15 mg/dL, was linked to relative CHD risks of 0.64 in men and 0.69 in women. The Emerging Risk Factors Collaboration,[357] a meta-analysis with over 300,000 subjects without CHD at baseline, found that rates of CHD per 1000 person-years in the lowest and highest tertiles of baseline lipid distributions, respectively, were 2.6 and 6.2 with triglyceride, 6.4 and 2.4 with HDL-C, and 2.3 and 6.7 with non–HDL-C. On the other hand, in a meta-regression analysis that included 108 randomized trials of lipid reduction upon outcomes[358] with about an equal number of participants at risk of cardiovascular events, simply raising the amount of HDL-C by 1.7 mg/dL (3.6%) had no effect upon CHD morbidity, CHD mortality, or total mortality after adjusting for the LDL-C levels.

In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), the ratio apolipoprotein B (apoB)/apolipoproteinA-I (apoA-I), discussed further below, predicted cardiovascular risk better than LDL-C or

HDL-C.[359] Of all available statins, rosuvastatin simultaneously produces the greatest increases in HDL-C and apoA-I, together with the best reductions in LDL-C and apoB.[360,361] In the ASTEROID trial,[241] HDL-C levels were inversely related to CHD progression during statin therapy as assessed using quantitative coronary angiography and using intravascular ultrasound (IVUS).[351] Negi and Ballantyne[362] plotted the change in percent diameter stenosis per year vs the on-treatment HDL-C level in an angiographic statin trial, which described a linear, monotone inverse relationship. The relative effects of rosuvastatin vs atorvastatin on atheroma volume, employing IVUS, is being compared in the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin vs Atorvastatin (SATURN), now in progress.[363]

HDL biology-function, quantity, and quality

HDL is a mixture of heterogenous particles synthesized in the liver, jejunum, on the surfaces of macrophages, and in serum. They vary in size, density (between 1.063–1.21 g/mL), composition, surface charge, and function. HDL shape ranges from discoid to spherical, depending upon its lipid composition. The biology of HDL is more complex than that of LDL, and capable of slowing atherosclerosis through several mechanisms. The number of regulators – genetic polymorphisms affecting synthesis of apoproteins, receptors, enzymes that remodel lipoproteins, and inflammatory markers that determine HDL-C levels, maturation, and function – are staggering, but multiple steps and regulators simultaneously provide additional therapeutic opportunities.[364] Over 75 different proteins are found within HDL populations that are concerned with lipid metabolism, complement activation, acute phase response; and protease inhibition.[365] Within the total HDL-C weight, the subfractions function differently, each with a specific biological function[366] which is partly dependent upon the triglyceride level. The complex proteasome and lipidosome of HDL particles, in constant flux, may alter individual HDL particle function as its composition changes. The most important protein component is apolipoprotein A-I (apoA-I), accounting for approximately 70% of HDL protein mass, with apoA-II comprising 15% to 20%. Hence, apoA-I is sometimes considered a surrogate for HDL-C. Physically, apo-AI occupies about 85% of the surface of HDL, and it is believed that HDL size is modulated by a twisting motion of the apo-AI molecule. Cross-linking chemistry and mass spectrometry data suggest that apo-AI adopts a symmetrical cage-like structure to hold the lipid cargo. HDL interacts functionally with scavenger receptor class B type I (SR-BI), a cell surface glycoprotein, and the resulting SR-BI signaling is important in hepatocytes, endothelial cells, macrophages, and platelets.[367]

The most significant atheroprotective function of HDL is reverse cholesterol transport (RCT). Preβ1-HDL, the lipid-depleted form of HDL, receives cholesterol from arterial plaque via macrophage ATP-binding cassette transporter ABCA1. In these enlarging particles, apoA-I accepts more cholesterol from the periphery, with the assistance of lipoprotein lipase and cholesteryl ester transfer protein (CETP), to become mature α1-HDL particles.[368] Eventually cholesterol is returned to the liver or to apolipoprotein B (apoB)–containing cholesterol-acceptor particles.[369] ApoA-I in HDL plays a major role in RCT: underexpression of apoA-I is antiatherogenic, and small peptides that mimic some properties of apoA-I may impede atherosclerosis and improve HDL function, even without a rise in HDL-C levels.[370] Raising apoA-I production also increases the the number of preβ1-HDL particles and is antiatherogenic. Various functions of HDL are summarized in Table 7.

These properties collectively provide significant pleiotropic protection against atherothrombotic disease, not only by modulating lipids, but also through non-lipid antioxidative, antiinflammatory, and antithrombotic mechanisms. Rosuvastatin produces the greatest rise in HDL-C compared to other statins, and for this reason may be favored, particularly in women, or in patients who are overweight, smokers, or glucose intolerant, all of which depress HDL-C levels. Proof, however, of improvement in clinical outcomes when HDL-C is raised in these settings, is presently lacking, and awaits data from ongoing studies.

"Dysfunctional" HDL

Unfortunately, quite apart from the torcetrapib experience, higher HDL-C levels, as mentioned above, are not always associated with improved cardiovascular outcomes.[377–381] When estrogen and progestins were administered in the Women's Health Initiative,[382] HDL-C rose 7.3%, but CHD risk increased by 29%. During pro-oxidative and inflammatory states, including CHD, diabetes, metabolic syndrome, infections, surgery, active rheumatic conditions, chronic kidney disease, obstructive sleep apnea, and other diseases, HDL may become "dysfunctional".[383] Rather than function as an antioxidant, it may even result in a pro-oxidant, pro-inflammatory phenotype;[384,385] HDL from patients with CHD may promote LDL oxidation.[386] HDLs from individuals

Table 7 Some functions of high-density lipoprotein (HDL)

- Participation in reverse cholesterol transport of cholesterol, through the ATP-binding cassette (ABC) transporters and additional mechanisms, is the most important vasculoprotective function. Since peripheral cells cannot metabolize cholesterol, it will accumulate unless carried back to the liver for disposal. Heterogeneous HDL particle subfractions are continuously exchanging moieties and interacting with other lipoproteins, lipolytic enzymes (hepatic and endothelial lipases), and transfer proteins (lecithin:cholesteryl acyltransferase, phospholipid transfer protein). A major feature of HDL remodeling involves transfer of cholesteryl ester from cholesterol-rich HDL in exchange for triglycerides from apolipoprotein B (apoB)–containing cholesterol-acceptor particles.[371] While the atherosclerotic process is affected by cholesterol efflux capacity from cultured macrophage foam cells, this property may be independent of the HDL-C level,[372] related more to its function, ie, quality, rather than quantity.[373]
- Protection and support of endothelium, through inhibition of monocyte chemotaxis, adhesion molecule expression, and enhanced nitric oxide production.[365]
- Prevention of LDL oxidation, involving two redox active methionine centers in apoA-I, paraoxonase-1 (PON-1) and paraoxonase-3,[374,375] as well as other component antioxidant enzymes contained in HDL, such as glutathione peroxidase, and platelet activating factor acetylhydrolase).
- Promotion of efflux of oxidized LDL from macrophages.
- Antiproliferative actions, particularly reducing apoptosis in macrophages.
- Anticoagulation, via inhibition of factors Va and VIIa and promotion of urokinase-dependent fibrinolysis.
- Inhibition of platelet activation and aggregation, which protects the endothelium and inhibits thrombosis.
- Augmentation of prostacyclin synthesis through activation of cyclooxygenase-2.
- Stimulation of endothelial cell migration and recruitment of endothelial progenitor cells at sites of endothelial injury.
- Reduction of inflammatory mediator expression.
- Participation in the immune system, through component complement proteins.[376]
- Inhibition of atherogenic remnant particle production, by maintaining VLDL-triglyceride homeostasis.
- Promotion of glucose uptake and fatty acid oxidation, tempering any rise in insulin resistance, along with upregulation of pancreatic insulin secretion.
- Mediation of vascular protection ascribed to 17β-estradiol, the most potent endogenous estrogen, via enhanced HDL-induced endothelial nitric oxide synthase 3 activity to increase nitric oxide release.

recently diagnosed with CHD, but not yet treated with statins, have a unique protein cargo, compared to HDL found in healthy control subjects.[365,387] There are many molecular mechanisms through which HDL may become dysfunctional, including changes in protein composition, change in antioxidant activity, overexpression of apoA-II, infectious processes and toxins, enzymatic modification of constituent HDL proteins and/or lipids, oxidation, interaction with inflammatory mediators, and others.

Common in vitro processes that may adversely affect the cholesterol efflux property of normal HDL are oxidation, preventing the maturation of HDL, advanced glycation of HDL, and chlorination and nitration of HDL by myoperoxidase (MPO). ApoA-I, the primary protein constituent of HDL, is a selective target for MPO-catalyzed nitration and chlorination in vivo. Such MPO-catalyzed oxidation of HDL and apoA-I selectively inhibits ABCA1-dependent cholesterol efflux from macrophages, which in turn promotes oxidation of LDL.[386,388] Other processes during inflammation that may impair HDL function are increased HDL catabolism, displacement of ApoA-I from HDL by the acute phase reactant serum amyloid A (which also impairs activity of lecithin:cholesterol acyltransferase, paraoxonase, and Lp-PLA$_2$),[389] lower synthesis of apoA-I[390,391] and decreased activity of platelet-activating acetylhydrolase and lecithin:cholesterol acyltransferase (LCAT).[392,393] During acute phase reactions beneficial proteins in HDL

particles other than ApoA-I may also be may exchanged for fibrinogen or soluble lipoprotein associated phospholipase A$_2$. In addition, changes in proteins that are not constituents of HDL, but are concerned with HDL metabolism, such as SR-BI, may be proatherogenic even when HDL-C is increased.[394] Finally, patients with polymorphisms in the promoter for hepatic lipase have higher HDL-C levels but raised risk for CHD.[376] Hence individual genetic mutations and metabolic status may result in critical loss of HDL function. Other genetic variations in which there may be a divergence of HDL-C levels and the anticipated inverse CHD risk are discussed by Tall et al.[395] Treatment of patients with nongenetic dysfunctional HDL with statins[396] or statins combined with niacin[397] may partially reverse the impairment in HDL function. Sorrentino et al[398] reported that HDL from diabetics was deficient in their ability to promote endothelial progenitor cell-dependent endothelial repair, increase endothelial nitric oxide expression, and produce endothelium-dependent relaxation. These defects were associated with raised HDL lipid peroxidation and MPO content, and could be improved with niacin therapy. Exercise is a frequently-overlooked, effective modality to partially repair defective HDL and raise HDL-C levels.

Interestingly, CRP and MPO have been linked together as predictors of prognosis in a number of cardiovascular outcome studies.[398] CRP has also been shown to stimulate MPO release in human polymorphonuclear cells and

monocytes in vivo, and may have significance in patients with acute coronary syndromes.[400]

With insulin resistance, the metabolic syndrome, acute inflammation, and in hypertriglyceridemia, more triglyceride-rich HDL is produced as a result of enhanced CETP activity. A number of events may lead to lower HDL-C and HDL-P, including remodeling of triglyceride-enriched HDL by hepatic lipase, resulting in enhanced binding, internalization, and degradation of HDL, as well as instability of these moieties with loosely-bound apoA-I, without major roles of either SR-BI or proteoglycans.[401–403] Moreover, the triglyceride-rich HDL uptake by SR-BI may be deficient, reducing the effectiveness of reverse cholesterol transport.[366] In diabetes, the typical lipid phenotype includes small, dense HDL particles, enriched with triglycerides and depleted of cholesteryl esters, which have lost 20%–50% of their antioxidative capacity.[404] This finding correlates with elevated levels of 8-isoprostanes, robust markers of oxidative stress.[405,406] Since patients with metabolic syndrome will not typically progress to overt diabetes unless there is pancreatic beta-cell failure, the recently-described potential role of deficient and defective HDL in the future loss of insulin secretion by beta cells through ABC transporters is of importance.[407] In addition, insulin resistance may increase HDL catabolism and renal excretion, adding to the difficulty of raising HDL-C levels in such patients.

HDL as a component of the immune system

Proteomic analysis of HDL[365] has identified more proteins involved with acute-phase response than are associated with lipid metabolism, consistent with the view that a major role of HDL is to inhibit inflammation. Moreover, a number of proteins within HDL regulate complement activation, which is known to have a role in atherogenesis.[408] Potential triggers of complement activation within atherosclerotic lesions include immune complexes, CRP, oxidized and glycated lipoproteins, apoptotic cells, cholesterol crystals, and possibly dysfunctional HDL.[409] Circumstantial evidence supports the hypothesis that HDL not only is responsible for cholesterol trafficking, but also plays a part in the immune system protecting against infection. Such a system envisions HDL assisting in the removal of apoptotic cells from inflamed and/or infected sites. Thus, in addition to the removal of cholesterol from macrophages, the additional exchange of proteins and lipid moieties between HDL and macrophages may regulate inflammation. Exposure of macrophages to bacterial endotoxin lipopolysaccharide (LPS) downregulates the transporters ABCA1 and ABCG1, thereby suppressing their ability to efflux cholesterol.[410,411] Any inflammatory mediators that use the same signaling pathways as LPS would inhibit reverse cholesterol transport. Direct proof was provided by administering LPS to human volunteers, which resulted in stimulation of acute phase reactants serum amyloid A and CRP. These changes were accompanied by remodeling of HDL, which became less able to accept cholesterol.[409] Further confirmation came from septic patients, in whom inflammation reduced the ability of HDL to accept cholesterol by 73% as compared with controls.[412] This proposal also fits with the larger notion that lipids are capable of activating circulating immune cells which may contribute to the pathogenesis of atherosclerosis.[413]

Heritability of HDL-C levels

About 40%–60% of HDL-C levels are heritable.[414] Aside from the ≈40 genetic polymorphisms in the *APOA1* gene which may contribute to variation in HDL function, genetic variation in genes encoding the many other substances involved in HDL metabolism, particularly CETP, appears to be clinically relevant. Genome-wide association studies demonstrate the strongest associations with HDL-C are found among *CETP* single nucleotide polymorphisms. For instance, the *B2* allele of the TaqIB polymorphism of *CETP* may be associated with recurrent cardiovascular events.[415] The strength of *CETP* gene polymorphisms upon HDL-C is also uninfluenced, at least in high risk patients, by dietary interactions, eg, the Mediterranean diet, or with obesity, smoking, diabetes, or alcohol use.[380] Although dysfunctional HDL may exist at all HDL-C levels, the association of high HDL-C with high CRP levels, especially in post-infarction patients, may be characterized by larger HDL particles, higher apoA-I and serum amyloid A levels, and suggests that further evaluation of HDL quality is warranted.[414] The full clinical significance of dysfunctional HDL awaits greater use of a relatively new cell-free laboratory evaluation of HDL function.[393,416]

An interesting application begins with an analysis from the INTERHEART study, which reported that South Asians have an unusually high prevalence of low HDL-C levels.[416] In South Asian immigrants, in whom metabolic syndrome is frequent, conventional risk factors, insulin resistance, and components of the metabolic syndrome, are insufficient to account for their raised CHD risk.[418] Using CIMT and a novel cell free assay and HDL inflammatory Index, Dodani et al[419] found that 70% of south Asian immigrants with subclinical CHD had dysfunctional HDL. It is hypothesized that a unique combination of genetic predisposition, high carbohydrate intake, lack of exercise, tobacco use, and low birth weight due to maternal malnutrition

suppresses the activity of Δ^6 and Δ^5 desaturases and lowers the levels of anti-inflammatory essential fatty acids in South Asians.[420]

Comprehensive discussions about HDL biogenesis, life cycle and function, are available elsewhere in greater detail.[364,382,403–406,421–425]

Potential of HDL modification to lower risk

Interest in raising HDL-C levels, or improving HDL function, continues in the ongoing search for methods to close the residual "risk gap".[403,424,426] The most effective available agent is niacin, but practical problems with flushing limiting the use of this agent are well-known. The failure of proatherogenic cholesteryl ester transfer protein (CEPT) inhibitor torcetrapib, which produced a 70.3% rise in HDL-C levels, but an increase in CHD of 21%, was due in large part to off-target toxicity characterized by aldosterone-associated hypertension, hypokalemia, and elevations in serum bicarbonate levels.[427–429] However, that disappointment has recently been replaced by some optimism. A preliminary report of the study Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) indicates that anacetrapib, another CETP inhibitor, produces an outstanding 138% rise in HDL-C levels, a 39.8% reduction in LDL-C, does not raise aldosterone levels, and may be associated with improved outcomes.[430–435] The beneficial lipid actions appear to be additive with those of statin drugs. CETP mediates exchange of lipids between HDL particles and other lipoprotein fractions. It remains to be shown whether the HDL produced by anacetrapib is biologically normal, cardiovascular events will be reduced, and safety will be demonstrated in a large randomized trial, which is now under way.[430] Dalcetrapib is a second nontoxic CETP inhibitor under investigation with potential to raise HDL-C and lower LDL-C.

An additional approach involves stimulating the endogenous production of apoA-I in patients with CHD in order to raise preβ1-HDL particle number and enhance RCT. A new oral agent, RVX-208, selectively induces nuclear transporter factors to induce hepatic ApoA-I synthesis, and has been shown to increase blood levels of both preβ1-HDL and mature α1-HDL. In the first report from the ASSERT (ApoA-I Synthesis Stimulation Evaluation in Patients Requiring Treatment for Coronary Artery Disease) study,[436] RVX-208 therapy raised apoA-I and HDL-C levels modestly, up to 5.6% and 3.2%–8.3% respectively, accompanied by an 11.1% to 21.1% rise in large HDL particles, actually less

than is associated with niacin therapy. Unfortunately there were also significant increases in hepatic transaminase levels, which may limit the future of this particular agent.[437]

While an additive effect of maximizing HDL-C levels along with reductions in LDL-C has been appreciated for over a decade,[438] the real potential of combining statins with other agents remains unknown. A beneficial effect upon atheroma burden was suggested in ASTEROID[230] and upon CIMT in ARBITER 6-HALTS[439] when using niacin.

Recently the AIM-HIGH trial[440] was stopped early by the NHLBI after 32 months. In this study, 3414 patients with cardiovascular disease, low HDL-C and high TG levels were given either simvistatin and a placebo, or simvistatin in adjusted doses and extended-release niacin 1500–2000 mg, with 515 of the patients in the treatment cohort receiving ezetimibe 10 mg if needed, to achieve LDL-C levels of 40 to 80 mg/dL. Although niacin lowered TG and raised HDL-C levels as expected, there was no effect on a composite endpoint of fatal or nonfatal MI, stroke, hospitalization for acute coronary syndrome, or need for revascularization procedures. A small, unexplained increase in the rate of ischemic strokes in the niacin group also played a part in the decision to halt the study. It is important to note that the patient population had well-controlled on-treatment LDL-C levels. Generalizing these findings to other patient groups, particularly to those with higher LDL-C levels commonly encountered, is presently premature. Full interpretation awaits analysis and publication of the AIM-HIGH study data. Hopefully, the results of the more definitive HPS2-THRIVE study[441] now in progress, involving 25,673 participants, will help answer some of the many questions raised.

However, these disappointing results suggest, as has been noted previously, that beneficial changes in surrogates such as risk factors do not necessarily mean improved outcomes, and now have significant implications for future drug investigations. In addition, the FDA currently approves new drugs based upon biomarker end points.

Despite the well-documented association of high HDL-C levels with cardiovascular protection, and low HDL-C values with poorer outcomes in atherothrombotic disease, pharmacological manipulation of global HDL-C levels is complex, probably not sufficiently specific with respect to the HDL molecule, and differs with each agent used.

Other lipid targets: non-HDL-C and lipid fractions

Compared to estimates of LDL-C, does measurement of apolipoproteinB, total cholesterol/HDL, apoB/apoA-1,

or non-HDL-cholesterol (non-HDL-C, total cholesterol – HDL-C), offer any advantage as a predictor, and as a therapeutic target? Early Framingham data showed LDL-C was predictive, but total cholesterol/HDL-C[442] and apoB/apoA-1 are equal, if not better, predictors.[443] Ratios show a stronger correlation with cardiovascular events than does LDL-C.[99,444,445] Since over half of all such events occur in apparently healthy persons without abnormal LDL-C levels, thinking beyond LDL-C has been a recent goal in order to improve both predictive ability and reduce residual risk. The lay press frequently mentions that up to 77% of patients with cardiac events have normal cholesterol levels, to which there is no satisfactory reply. Moreover, the relatively high proportion of statin-treated patients hospitalized for new events, even though a significant number of them are already at LDL-C goals, is a further embarrassment.[355]

The estimated LDL-C derived from the Friedewald formula not only introduces error, and does not reflect all atherogenic particles, but the need for a fasting sample is inconvenient. Without the need to fast, non-HDL-C is easily derived from the prevalent lipid profile.

Non-HDL-C is strongly associated with cardiovascular events[446,447] and is sometimes considered a proxy for apoB. When calculated from the standard lipid profile, it measures the amount of cholesterol contained in all atherogenic lipoproteins (excluding any proatherogenic HDL) – LDL, IDL, VLDL, and Lp(a). On the other hand, apoB reflects the number of circulating atherogenic particles, and is expressed in mg/dL. LDL particle number (LDL-P) is the number of LDL particles per liter of plasma, expressed in nmol/L. In healthy people non-HDL-C may equal apoB and LDL-P for accuracy in risk assessment.[448,449] However, when HDL levels are low, triglyceride values are high, and in patients with diabetes or metabolic syndrome, LDL-P and apoB are much better indices of cardiovascular risk.[359,440–452] Compared to the 1970s and 1980s, an increasingly greater proportion of patients being evaluated are overweight, have higher triglyceride (TG) levels and small, dense LDL particles. With an abundance of triglycerides and TG-rich particles, these patients overproduce VLDL in the liver, which accounts for the increase in small, dense LDL and their low concentrations of HDL-C.[453,403] As the number of individuals with visceral adiposity in the population – now at 53% – increases, the accuracy of standard lipid profiles to predict risk diminishes, particularly in overt diabetics, since the discordance between LDL particle number and LDL-C enlarges as triglyceride values rise

above ≈160 mg/dL. An American Diabetes Association/American College of Cardiology consensus statement[454] considered this discordance and some limitations of the method. A more recent position statement by the American Association for Clinical Chemistry favored LDL-P as an accurate indicator of risk, and reviewed the advantages of monitoring particle number in order to reduce residual risk.[455] Tests for LDL-P are FDA approved and their predictive ability was confirmed in the MESA study.[456] These statements reflect that risk is better captured by apoB or LDL-P than by non-HDL-C, which itself may be discordant with apoB in about one-third of patients, and many lipidologists believe non-HDL-C is superior to LDL-C. It is important to note that the effect of individual statins upon lipid subfractions may differ,[457] as may the relative effect upon LDL-P. In 318 patients with dyslipidemia and the metabolic syndrome, for instance, rosuvastatin was found to be superior to atorvastatin in lowering LDL-P.[458] Further discussion is available in the recent contribution by Dayspring et al.[459]

The NCEP-ATP III[153] presently recommends LDL-C as the primary target to be monitored, but after the LDL-C goal is reached, and if triglyceride levels are ≥200 mg/dL, non-HDL-C is set as a secondary goal at 30 mg/dL higher than the LDL goal. The fourth Joint European Societies Guidelines[31] estimates risk of fatal cardiovascular events using SCORE,[150] which is similar to Framingham but uses total cholesterol/HDL-C as the primary target. The Joint British Societies (JBS 2) guidelines[293] uses similar criteria and the total cholesterol/HDL-C, to estimate 10-year risk, but employs LDL-C treatment targets.

Using Framingham data, Liu et al[460] found that VLDL-C was a significant predictor of cardiovascular risk, and that non-HDL-C was superior to LDL-C in predicting risk. In a large study of healthy Japanese men and women, the total cholesterol/HDL ratio best reflected long-term changes in lipid risk with the least within-person variation when compared to LDL-C.[460] The superiority of measuring ratios of pro- to anti-atherogenic lipoproteins with respect to errors was also supported by Glasziou et al.[461] An analysis of INTERHEART data found that non-fasting apoB/apoA-I was superior to other cholesterol ratios for estimation of the risk of myocardial infarction for all ethnic groups, ages, and in both sexes.[463]

The causal role of elevated lipoprotein(a) [Lp(a)] in premature cardiovascular disease has also been of interest. Presently Lp(a) elevations are probably not being given sufficient attention, and many are missed in routine lipid

measurements, yet its relationship with CHD is robust and specific. The EAS Consensus Panel has critically reevaluated Lp(a) as a risk factor, and supported screening patients at intermediate or high CHD risk with premature CHD, familial hypercholesterolemia, a family history of premature CVD and/or elevated Lp(a), recurrent CHD despite statin treatment, ≥3% 10-year risk of fatal CVD according to European guidelines, and/or ≥10% Framingham risk.[464]

In summary, LDL-C has limitations which are well recognized. ApoB is a better predictor than LDL-C,[465] is not generally available, and has not been embraced clinically. Non-HDL-C, a proxy for apoB, measures the cholesterol content within atherogenic lipoproteins and is easily derived from standard lipid profiles, but may not reflect the full residual risk when particle number is discordant. Non-HDL-C is incorporated in several guidelines. LDL-P is the most accurate when predicting risk, is only available through independent laboratories, and reimbursement is irregular.[452,466] Targets for the highest risk patients are LDL-C < 70 mg/dL, non-HDL-C <100 mg/dL, apoB < 80 mg/dL,[454] and perhaps LDL-P ≤ 1000–1100 nmol/L.

Risk and the significance of CRP and inflammation in prevention and pathogenesis

Epidemiological, pathological, clinical, and imaging studies have constructed an evolving model of atherothrombotic disease, spanning the period from biochemical and physical triggering of endothelial dysfunction to rupture of a vulnerable plaque. Although atherothrombosis was once considered to consist of simple lipid and "plumbing" problems, a unifying concept of the role inflammation is now supported by considerable data in both the clinical and preclinical sciences. The numerous beneficial anti-inflammatory pleiotropic actions of statins and results of the JUPITER study suggest inflammation matters clinically.[467–472]

In a number of conditions and processes, including chemical injury, hypercholesterolemia, hypertension, endothelial dysfunction, cytokine stimulation, oxidative stress, and others, trapping of chemically modified LDL occurs within the arterial wall.[473] Inflammatory monocyte recruitment,[474] under the influence of cytokines and other protein mediators, leads to the expression of scavenger receptors for altered LDL and the formation of foam cells.[467] C-reactive protein is a biomarker of inflammation, with hepatic expression driven by interleukin-6 (IL-6), the "messenger" cytokine (notifying and activating the immune system after tissue injury). High CRP levels are closely associated not only with infections but with vascular disease, cancer, and autoimmunity. Evidence underpinning the close associations of CRP levels with vascular disease and its predictive value are the result of the accrual of knowledge over a long period of time by many investigators.[15] High-sensitivity C-reactive protein (CRP) is able to discriminate levels of the protein at concentrations far below the greater variations associated with generalized inflammation. There is evidence that CRP concentrations reflect aspects of inflammation related to lifestyle, such as visceral obesity,[475,476] and the metabolic syndrome,[477,478] lack of physical activity,[479] vegetable and fruit consumption,[480] omega-3 fatty acid ingestion,[481] and alcohol intake,[482,483] all of which may not be fully captured by other risk markers, such as LDL. In fact, despite great attention to the genetic variations influencing CRP levels, lifestyle is actually the more significant determinant.[484] Further, CRP levels are associated with all 7 health behaviors and factors that were cited by the AHA as components of ideal cardiovascular health (Table 2).[2]

The associations among visceral adiposity, diabetes, metabolic syndrome and inflammatory markers,[341,485,483] as well as the relationship between the first three entities with elevated CRP,[484] are well-known. The link between the metabolic syndrome and atherosclerosis involves elements other than insulin resistance, and CRP levels correlate with both the diagnosis of metabolic syndrome and the number of risk components.[488] Adipose tissue releases IL-6 which stimulates CRP synthesis, but is also a significant source of CRP itself. Weight loss in obese women lowers CRP and raises adiponectin concentrations.[489] CRP correlates with insulin levels,[490] and the Mediterranean diet lowers insulin resistance and CRP levels.[488] The Look AHEAD (Action for Health on Diabetes) study recently reported on a large cohort of overweight diabetic women whose CRP levels fell markedly in response to intensive lifestyle intervention resulting in weight loss over a 1 year period.[492]

While elevations of IL-6 and CRP are associated with illnesses that are expected to shorten life, low values, while not a guarantee of freedom from diabetes or CHD, may generally reflect better health. The Rancho Bernardo Study[493] found that higher concentrations of these inflammatory markers predicted shorter survival time and reduced lifespan among older men. In addition, in various clinical situations, CRP levels correlate with mortality[494,495] and survival,[496] with strong predictive ability in many cardiovascular scenarios.[497–503] In the Emerging Risk Factors Collaboration,[497] a meta-analysis of 54 prospective studies, CRP correlated better with future vascular events than either blood pressure or cholesterol.

Although the prognostic value of CRP in a broad population of patients at high risk for ischemic events is accepted, clinical utility of using CRP in treatment remains debated.[504]

CRP, as a pattern recognition molecule capable of activating complement, functions as a regulator in the innate immune system, the latter increasingly recognized as a participant in atherosclerosis.[471,472,474,505,506] Oxidized LDL and oxidized phospholipids on surfaces of apoptotic cells are recognized by macrophage scavenger receptors, have proinflammatory and proatherogenic properties,[507] and CRP binds to both through recognition of the phosphorylcholine moiety in oxidized phospholipids.[508] The innate immune system appears to prime normal protective T cell-mediated immunity,[509] which is involved in the inflammation associated with the metabolic syndrome[510] and hypertension,[511] two conditions in which CRP levels are frequently elevated. Clinically, the involvement of inflammation may explain the correlation of CRP elevations and early atherosclerosis detected by CIMT.[512,513]

In addition to inducing release of proinflammatory cytokines from monocytes, upregulating NADPH oxidase activity, and promoting endothelial dysfunction, CRP appears to have a role in priming differentiation of human monocytes toward a proinflammatory M1 phenotype, a critical event in the pathogenesis of atherosclerosis. Transformation of monocytes, or M1 polarization, may be regarded as an on-off switch in the balance between pro- and anti-inflammatory processes, and lead to macrophage maturation, further expression of inflammatory cytokines, and tissue destruction. Macrophage infiltration of adipose tissue in obese animal models and humans is associated with both an absolute rise in the number of M1 polarized macrophages and reduced sensitivity to insulin. M1 monocytes also infiltrate atherosclerotic lesions.

Recognition of modified extracellular matrix proteins by the innate immune system results in collateral blood vessel remodeling to accept additional blood flow. The encounter of agonists and toll-like receptors (TLR), another class of pattern recognition receptors, specifically TLR2 and TLR4 on monocytes and extracellular matrix fragments, leads to inflammation through the activation of the nuclear factor kappa B and interferon response factor pathways, in turn increasing the expression of proinflammatory cytokines, chemokines, matrix metalloproteinases, interferons, growth factors, and other molecules involved in arteriogenesis. There is a dynamic interaction between reduced blood flow, modified extracellular matrix proteins, and collateral vessel growth/vascular remodeling, in which TLR, monocytes and T-lymphocytes are involved.[514,515]

The recent recognition of the important and extensive role of the innate immune system in arteriogenesis, the increase in diameter of preexisting arteriolar connections, arterial remodeling during ischemia and atherosclerosis adds yet another dimension to pathogenesis of the disease.[516] The full role of this process as a mechanism which protects against ischemic injury has yet to be determined.

Strategies proposed to improve cardiovascular risk reduction

The concept of risk factors, introduced by the original Framingham investigators in 1961, essentially established preventive cardiology. Risk factors are now accepted antecedents of atherosclerosis whose levels predict subsequent cardiovascular events and are targets for therapy. The current approach to cardiovascular risk screening is summarized in a state-of-the-art paper by Berger and associates.[52]

Within the past few years there has been a reevaluation of reducing risk in the general population, and the central unanswered question is: how can people who will eventually have cardiovascular events be identified and their risk lowered? There is no ideal or "gold-standard" risk equation for assessment, nor a drug-response equation for treatment. Current issues in primary prevention of CHD include the long incubation period; methods of evaluating risk in the population; population-based vs individual risk-based approaches; role and refinement of global risk factor scores; choice and merits of nontraditional risk factors; multiple biomarker panels; imaging techniques in evaluation and ongoing therapy; value of advanced lipid testing; weights given to traditional risk factors, cutoff values and treatment targets, particularly LDL goals in guidelines; use of statins in primary prevention; reasons for low patient adherence with evidence-based therapies; causes of "clinical inertia" and lack of physician compliance with guidelines; and the etiologies, extent, and minimization of residual risk. Within this period, there have been several suggestions based upon models, proposals, and clinical protocols contributing to the dialog, enumerated below with additional commentary.

Encourage population-based interventions emphasizing primordial prevention

Primordial prevention is the unchallenged method of choice for risk reduction, far more efficient than pharmacological intervention. A long tradition of epidemiological data has accumulated since the pioneering report of de Lorgeril

et al concerning the Mediterranean diet[517] and the Lyon Diet Heart Study.[518] About that same time, Stamler and coworkers[519] published a series of 2 cohorts totaling 366,000 participants and reported that just 4 favorable risk factors (BP < 120/80 mm Hg, TC < 200 mg/dL, abstinence from tobacco, and no diabetes) was associated with a 72%–92% lowered cardiovascular mortality and an additional 5.8–9.5 years of life. Since then, there have been a great number of ongoing investigations and exceptional contributions affirming the favorable impact of the Mediterranean diet pattern and physical activity upon all-cause longevity, cardiometabolic, and other chronic diseases.[520–523] The evidence supporting the effectiveness of lifestyle modification upon cardiovascular outcomes is summarized elsewhere[2,11] and continues to amass.[40,524]

While primordial prevention is most desireable,[177,525] social and political barriers are considerable, and current individual resistance to major behavioral modification is complex and not well understood. Perhaps the milieu of modern life has de-emphasized personal responsibility – or made it so difficult – for so long that the public now dismisses attempts to reverse these concepts as impractical, imposing, irrelevant, or unworthy. The message that medical care is unlimited and uniformly successful at all stages of disease may also unwittingly reduce motivation for personal health ownership. It would therefore appear that public re-education is fundamental for further progress, rather than a wasteful endeavor.

At the same time, it has been suggested that continued attempts to reduce cardiovascular risk without the addition of population-wide prevention is destined to fail.[526] Plainly, furnishing entire populations with unlimited scans, statins, stents, and surgery is not the best answer. For this reason, and because it is premature to declare risk reduction programs a failure without further data or better alternatives, interest in refining and continuing comprehensive primordial prevention, including education and counseling, continues. A combined, multipronged, intensive approach to cardiovascular risk reduction using many techniques will be necessary.

Change the lipoprotein or lipid fraction that is monitored and targeted

As discussed above, non-HDL-C measures all atherogenic lipoproteins which contain apolipoprotein B, including LDL-C, very low-density lipoprotein cholesterol (VLDL-C), intermediate-density lipoprotein cholesterol (IDL-C), lipoprotein(a), chylomicrons, and chylomicron remnants. Non-HDL-C provides a more complete measure

of atherogenic particles than LDL-C and is believed to be superior in capturing residual risk and ability to predict cardiovascular events. Evidence now indicates that monitoring and targeting non-HDL-C can better predict cardiovascular events than use of LDL-C,[326,446,527,528] with up to twice the yield.[529] Advanced lipid testing may identify abnormalities in small, dense LDL particles, LDL-P, HDL2[b], and Lp(a) fractions in a surprising number of patients. Ideally, all lipid pathology should be addressed to minimize cardiovascular events.

Use "lifetime risk" rather than global 10-year risk scores, and start treatment much earlier

Estimates of lifetime risk assessment offer an important tool which may be used in conjunction with 10-year risk. With 56% of American adults scoring a low 10-year, but a high lifetime risk, this issue has received increasing consideration.[213] The difference becomes of particular concern in both young and asymptomatic people.[185,530] Lifetime risk may be estimated after Lloyd-Jones[27] or as a 30-year Framingham risk that accounts for competing risks.[531] In the JUPITER study of rosuvastatin in primary prevention, about half of the participants had a 10-year FRS < 10%, but a significant number benefited when their LDL-C was lowered from a mean of 108 mg/dL to a mean treated value of 55 mg/dL, reflecting the degree of unrecognized cardiovascular risk in an asymptomatic population.[532]

Using lifetime risk, beginning treatment early, and continuing therapy over an extended period, matches the timing of treatment to the time of disease progression, which is amply supported by newer data concerning pathogenesis of the disease.

Give statins to intermediate-risk individuals guided by CRP – dual targeting using JUPITER criteria

The JUPITER study[532] involved 17,802 individuals with LDL < 130 mg/dL and CRP ≥ 2 mg/L, free from diagnosed cardiovascular disease or diabetes, and included women, minorities, and the elderly. The mean LDL-C was ≈100 mg/dL, and the average FRS was 11.6%. Treatment with rosuvastatin 20 mg, compared to placebo, was associated with a statistically significant 54% reduction in myocardial infarction, a 47% reduction in need for angioplasty or bypass surgery, a 48% reduction in stroke, a 43% reduction in venous thrombosis, and a 20% reduction in all-cause mortality. The JUPITER study group concluded that primary prevention patients

with high CRP values were at greater risk despite acceptable LDL-C levels and low Framingham Risk Scores, and such individuals benefited from rosuvastatin therapy. The 5-year number to treat was 25, which compared favorably with other primary prevention methods, such as hypertension.

JUPITER definitively established the efficacy of rosuvastatin in primary prevention.[532] The controversy surrounding the JUPITER trial is discussed elsewhere.[15] Proponents and critics agree that the benefits of rosuvastatin in JUPITER-eligible participants, however, were real. The US Food and Drug Administration approved new indications for rosuvastatin to include asymptomatic JUPITER-eligible individuals with 1 additional risk factor. The Canadian Cardiovascular Society guidelines recommend testing for CRP, and using statins in persons with low LDL-C and high CRP levels at intermediate risk. The joint European Society of Hypertension/European Society of Cardiology Guidelines suggested CRP measurements be included in the assessment of risk in hypertensive patients.[533] In a recent post hoc analysis of JUPITER requested by European health authorities,[534] patients with an estimated SCORE risk $\geq$ 5% or FRS score $>$ 20% had significant reductions of 43%–53% reduction in the risk of MI, stroke, or cardiovascular death when treated with rosuvastatin, compared with those treated with placebo. SCORE, as noted above, does not include CRP measurements. In their decision, the European Medicines Agency compromised between scientific evidence and economics, and their extension for rosuvastatin use in high-risk patients was admittedly arbitrary.

A recent reanalysis[535] of cost-effectiveness demonstrated that rosuvastatin in JUPITER-eligible patients had an incremental cost-effectiveness of $25,198 per quality-adjusted life year (QALY) gained compared to customary care. When applied only to patients with an FRS $\geq$ 10%, the incremental cost-effectiveness became $14,205 per QALY. Unknowns with respect to long-term effects cloud the issue, since sustained effects are assumed, but data is lacking.[536] All proposals to improve risk refinement and lower risk burden, even nonselective administration of generic statins, will incurr expense.

The continuing debate about the use of statins in primary prevention, while quite apart from the JUPITER trial, has been connected to JUPITER for unclear reasons.[15] Whenever use of statins in primary prevention is discussed, the cholesterol hypothesis, saturated fat-cholesterol link, JUPITER, and side effects of statins are also commonly argued de novo. Often in blogs and nonacademic publications the information presented is not evidence-based, but internet-based. Some authors have asserted that three-fourths of patients who take statin drugs for primary prevention – a significant number of all who use statins – do not benefit.[292,537] Several guidelines from the American College of Cardiology, American Heart Association, and European Society of Cardiology disagree with this view. It has also been said that the JUPITER study masked or caused a loss of appreciation for primordial prevention[23,24] but the debate concerning statin effectiveness in primary prevention predated the publication of JUPITER and is ongoing.[36,298] No responsible cardiologist questions the value of primordial prevention before pharmacologic therapy. Individuals following a Mediterranean or Paleolithic diet who achieve ideal cardiovascular prevention would not need any therapy.[538] The reality is that adherence to the Mediterranean diet, or any other lifestyle leading to ideal cardiovascular health, has fallen markedly even in areas of traditional origin – the Greek Islands – in favor of Western fare, accompanied by a corresponding increase in risk for CHD. Reversing this deterioration is the unmet challenge. The continuing fall in ideal cardiovascular health associated with poor lifestyle choices and the dual epidemics of obesity and diabetes are unrelated to the availability of statins or any particular application.

When lifestyle modification fails in individuals who are JUPITER-eligible, with "normal" LDL-C and high CRP levels, clinicians have an additional choice of using rosuvastatin to improve outcomes. This approach is simple, noninvasive, easily repeated, and does not involve radiation. CRP has been found useful in reclassifying risk in several series including the Framingham Heart Study, the Women's Health Study, the Physicians' Health Study, the Uppsala Longitudinal Study of Adult Men, the MONICA-Augsberg cohort, the EPIC Norfolk study, the Atherosclerosis Risk in Communities study, and the Heart and Soul cohort. The 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults,[32] concluded that measuring CRP levels in JUPITER-eligible patients can be useful in the selection of patients for statin therapy, ie, that beginning statins in this population is reasonable, with recommendation Class IIa, Level of Evidence (LOE) of B.

Increase utilization of imaging: CIMT and CAC

Carotid intima-media thickness (CIMT)

CIMT is a useful, noninvasive, inexpensive, reproducible but operator-dependent, predictive, radiation-free, office-based technique.[539–542] An increase in CIMT predicts the risk of cardiovascular events, but associations with cerebral arteriial events are stronger than with coronary events, relating more

to variability and differences in atherosclerosis between the two arterial beds than to limitations in CIMT measurements. CIMT also provides information about noncalcified plaque.[543] CIMT may detect significant atherosclerosis in patients with a zero calcium score, more likely to be young and/or female. Of 89 patients with a CAC of 0, mean age 48 years, CIMT found evidence of carotid atherosclerosis in 42 (47%; 95% CI: 37%–58%).[544] CIMT may be more sensitive than CAC in detecting subclinical atherosclerosis in a younger population, when treatment would produce greater benefits over time. It is believed that since calcification occurs later in the natural history of the disease, earlier stages of atherosclerosis – vulnerable plaque and noncalcified "inflammatory" lesions – may be found by CIMT. Therefore, CIMT may also find particular application in young healthy individuals, as well as in women and black patients.[545] Once detected, however, coronary calcium is a much more powerful predictor of future coronary events than CIMT.[219]

CIMT has also been used effectively to monitor disease progression in individual patients, and in studies comparing properties of subgroups within a given diagnosis. In diabetes, for instance, CIMT has contributed to the understanding of vascular disease in people with normal glucose tolerance, impaired tolerance, overt diabetes, in those with hypertension, microvascular and other complications, and after treatment with hypoglycemic, antihypertensive, lipid-lowering and anti-platelet agents.[546] As mentioned above, CIMT may be more appropriate as a surrogate in some populations and less adequate in others.[547] Since the intima may thicken, and the media may become hypertrophic with age, not all elevations in CIMT in the elderly are due to atheroma.

Despite widespread use of CIMT serially to assess effects of therapeutic agents, a recent meta-analysis suggests limited usefulness for this purpose. Costanzo et al[548] undertook a weighted random-effects meta-regression analysis to test mean and maximum CIMT changes and hard outcomes. They included 41 trials totaling 18,307 participants. Despite significant reductions in CHD and CVD events, as well as in all-cause mortality induced by various interventions, they found no significant relationship between CIMT regression and events in any of these categories. The surprising conclusion was that neither regression nor progression of CIMT changes correlated with, or predicted, changes in major cardiovascular events associated with various drug treatments in patients at intermediate to high cardiovascular risk. These findings, which disagree with the bulk of prior experience, may be due to limitations of the meta-regression analytic method and the limited length of follow-up in the

Table 8 Characteristics of CIMT and CAC by CT

Quality of interest	CIMT (Ultrasound)	CAC scoring (CT)
Area	Intima-media	Calcified lesions
Radiation	None	0.7 mSv for EBT and 3–5 mSv for helical CAC (may vary 10-fold up to 10.5 mSv)
Sensitivity	50 to 70	85
Specificity	60 to 80	75
Hazard ratio for incident CVD event per SD increment change title	1.3	2.1
Reclassification improvement	Unknown	Yes
Discrimination improvement	Uncertain	Yes
Operation simplicity	++	+++
Operation reproducibility	User dependent	Automated
Approximate cost	US $200	US $300–$600
Capitalization and access	Low-within office and research access	High-larger facility access

Abbreviations: CAC, coronary artery calcium; CT, computed tomography; CIMT, carotid intima-media thickness; EBT, electron beam tomography.

component studies. Replication of the data and explanation of inconsistencies are required.

Nonetheless, CIMT provides an excellent risk prediction tool which may be repeated easily. In the past 10 years, seven guidelines or consensus statements have recommended using CIMT or carotid plaque detection to predict risk.[549] The USPSTF was not one of them.[550] Among several potential applications of CIMT, appropriate use criteria rated seven as appropriate, 16 as uncertain, and 10 as inappropriate.[364]

The 2010 ACCF/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults[32] have assigned a Class IIa, LOE B recommendation for CIMT for risk assessment in asymptomatic individuals in the FRS intermediate risk category. Additional mention was made that recommendations for equipment, technical approach, operator training and experience for performance of the test must be followed. Some characteristics of CIMT and CAC are compared in Table 8.

Coronary Artery Calcium scoring (CAC)

Together with traditional risk factors, CAC also increases discrimination between patients who will or will not have future events, and improves prediction.[551,552] CAC is noninvasive, sensitive, automated, involves radiation exposure (0.7–1.8 mSv depending upon method), and is somewhat more expensive per test than CIMT, requiring greater operating costs and a much larger capital outlay. A great deal of data and a number of reviews have recently been published concerning

the potential of CAC.[193–195,553–562] Special note should be made of the Society for Heart Attack Prevention and Eradication (SHAPE) guideline,[560] advocating early use of CAC in primary prevention patients [563,564] with updated commentary.[553]

Nasir et al,[565] reporting on of 1,611 asymptomatic individuals (67% men, mean age: 53 ± 10 years) who had CAC scores performed using single electron beam tomography, found that 59% of those with a CAC score >400 and 73% with a score >75th percentile would not have been eligible for statins using NCEP ATP III criteria. CAC scores were able to reclassify 55% of patients classified as FRS-low risk to an intermediate risk category, and 45% of those with intermediate risk to high risk. In terms of biological age, linear prediction models showed that a CAC score <10 led to a reduction in observed age of 10 years in asymptomatic individuals over age 70, compared to those with a CAC score >400, which added up to 30 years of biological age to younger patients.[566] Hence, a CAC of 0 has been called a "priceless" possession.[567]

A patient with some calcium has a relative risk ≥ 2 compared with a CAC of zero, and in those with a CAC > 100, the relative risk is >4. The greatest value of CAC scoring is in patients classified in the FRS intermediate risk group. The reclassification rate is 54%, with 16% moving into the high risk category. In the Rotterdam study,[556] the relative risk of a CHD event between the highest 11% and the lowest 50% of the calcification score distribution was 8.3. For individuals with a CAC of zero, the practitioner may be more inclined to avoid statins and aspirin, given their finite complication rates. A CAC over 100 might suggest aggressive LDL-C lowering with continuation of aspirin. For very high CAC values, over the 75th percentile for age and gender, vigorous medical therapy is indicated with further work-up according to guidelines.

The MESA study[219] found the association between incident cardiovascular events stronger with CAC than with CIMT (hazard ratio for incident event per SD increment 2.1 and 1.3 respectively), and an area under the receiver operating characteristic curve of 0.81 and 0.78. While a popular subject for debate has been the relative advantages of CAC and CIMT for risk stratification in primary prevention,[568] these techniques, as well as CRP measurement, are complementary clinical tools, rather than competitors.

For detection of plaque regression, CAC may not be reliable. Some reservations have also been voiced about the clinical usefulness and cumulative radiation exposure in heart patients.[199,224,568–579,633] While the radiation exposure per procedure is now lower with new technology, exposure is uneven. Cumulative radiation exposure in adults, even in children, is rising, since imaging for all purposes is becoming common.[580–582] In view of the long delay between exposure to ionizing radiation and development of cancer, as well as its certainty, researchers have suggested that enthusiasm for cardiac imaging should be tempered.[579]

Another potential distraction is the finding of "incidentalomas" on imaging – about 20%–53% of electron-beam CT and 15%–67% of multidetector row CT report extracardiac lesions. About 5%–11% are significant, with 4%–25% of them potentially significant.[583] Additional tests, expense, inconvenience, professional time, and patient anxiety may follow. The US Preventive Services Task Force (USPSTF) disfavors CAC because it leads to additional testing and may funnel asymptomatic individuals to catheterization laboratories. In contrast, advocates cite some tests and revascularizations that may also be avoided. When patients are found to have a zero calcium score, less aggressive LDL-C targets translate into less expensive protocols with generic statins, but the quantitative significance of this remains uncertain.

An intriguing study from Johns Hopkins School of Medicine reported on the use of CAC in 950 healthy male and female participants with LDL-C < 130 mg/mL and CRP ≥ 2 mg/L from the MESA population over a 6-year period.[221] About 47% had a calcium score of 0, 28% had a calcium score of 1 to 100, and 25% were in a high-risk group with a calcium score over 100. About 75% of the deaths related to CVD events occurred in the highest-risk group. According to these data, in individuals with a calcium score of 0, the CHD event rate was 0.8 per 1000 patient-years, the number needed to treat (NNT) to prevent one CHD event was 549, and for a CVD event, NNT was 124. In the group with a score between 1 and 100, the event rate was 4.8 per 1000 patient-years. In the group with CAC > 100, the CHD event rate was 20.2 per 1000 patient-years, and the NNT to prevent 1 CHD event was 24, and for 1 CVD event, 19. The hazard ratio for a CHD event in the highest-risk group of 24.8 (95% CI 2.5–14.6) is indeed convincing. Placing this information in perspective will require further randomized trials. These data clearly show that a significant amount of cardiovascular risk and incipient pathology exists within the asymptomatic, nondyslipidemic population who do not presently qualify for further medical attention. More patients are now presenting with LDL-C values that are not especially elevated, which may elicit undertreatment with statins (see above discussion).

The use of CAC as a noninvasive test for risk stratification of emergency department (ED) patients with chest pain in order to decide whether to proceed with coronary angiography or discharge is a different, although similarly controversial,

issue than stratification of asymptomatic individuals classified as intermediate risk using FRS. Sarwar and colleagues[584] reported data from 18 studies that revealed any CAC had a pooled sensitivity and negative predictive value of 98% and 93%, respectively, for finding significant CHD on invasive coronary angiography. Even so, Garcia and Fuster[585] noted that from those same data, while the incidence of obstructive CHD in chest pain patients with zero CAC scores is small, at 7.2% it is not negligible. Candemartiri et al[586] found that CAC scoring was inadequate when compared to computed tomography coronary angiography (CTCA) in excluding CHD in asymptomatic, high-risk patients. Gottlieb et al[587] reported that the absence of coronary calcification (CTCA) had a positive predictive value of 81%, and a lower negative predictive value of CAC of 68%, and therefore a zero CAC score does not reliably rule out significant CHD in patients being referred for coronary arteriography. Of those, about 20% had a high pretest probability of CHD, 75% had an intermediate, and 5% had a low probability of CHD. In an accompanying editorial, Redberg[588] commented the practice should be discouraged, largely due to the failure to predict 19% of patients with CHD as well as a finite radiation risk. While the radiation for CAC is minimal, with a median value of ≈3 mSv, roughly equal to that of a mammogram or 100 chest x-rays, the variation is considerable (2–7 mSv),[224] and multiple scans in the same patient are becoming more common. Generally, patients' perceptions of cumulative CT radiation risk are inaccurate.[589] Three years ago, the number of future malignancies from CT scans done in 2007 was estimated at ≈29,000, corresponding to some 15,000 deaths.[590] In contrast, supporters argue that CAC scores are of immense help in evaluating chest pain in the ED and elsewhere.[195,233,567,592–594]

A summary of the utility of CAC in risk evaluation[594] concludes, as do guideline writers, that the absence of detectable coronary calcium is associated with a favorable prognosis, but is imperfect and carries a limited (92%) warranty of about 4.1 ± 0.9 years.[223] While CAC measurement does refine risk stratification above that provided by the FRS in asymptomatic, intermediate-risk patients, whether doing CAC scoring earlier in more patients will result in improved long-term clinical outcomes has yet to be decided, and doing so will be difficult. Restricting use based upon lack of such data may be too stringent a requirement. A larger question is whether CAC used to assess higher risk is superior to a population based strategy. In response to correspondence regarding the role of CAC scoring, Redberg[595] opined that, despite two decades of study, data showing patient benefits from information derived from the CAC are still lacking, and that for this reason, the

USPSTF concluded the evidence regarding CAC score is insufficient to assess the benefit to risk ratio.[550]

Baseline measurements of CAC have received a Class IIa, LOE B recommendation (reasonable) for those at intermediate (10%–20% 10-year) risk or Class IIb for individuals at low to intermediate risk by the 2010 ACCF/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults, and for those at low to intermediate (7%–10% 10-year) risk, a Class IIb, LOE B recommendation.[32] No recommendations have been made for CAC progression for assessing treatment. CAC progression may provide even more valuable information, but also requires sequential CT scans with additional radiation exposure, together with other limitations.[596]

Allocate statins to low- and intermediate-risk individuals using specified risk thresholds, rather than ATP III or JUPITER criteria

There is some evidence that extending statin therapy to Framingham low- and intermediate-risk individuals may be cost-effective at all levels of LDL-C.[316,597,598] Reservations about such a policy arise from potential side effects and expense. As was done in JUPITER, a CRP ≥ 2.0 mg/L can be used to identify those persons with higher risk in a population without ATP III-defined dyslipidemia who might benefit from statin therapy. A different approach to efficient lowering of cardiovascular risk was suggested by Lee et al.[302] These investigators examined the cost effectiveness of strategies following three hypothetical cohorts of individuals starting at age 40 with normal lipid levels and no diagnosed coronary artery disease, peripheral arterial disease, or diabetes. Their Markov decision analytic model compared three situations using: a) ATP III guidelines, a current popular strategy; b) CRP screening in JUPITER-eligible patients, followed by statin treatment only for those with CRP elevations, as suggested by the JUPITER study; and c) a strategy of starting statin therapy at specified predicted risk thresholds without first performing any CRP testing. Assuming that the relative risk reduction in events by statins is uniform whatever the baseline risk might be (statins are equally effective regardless of CRP status, providing benefits in low-risk individuals with normal LDL-C and CRP levels) the most cost-effective strategy was c). Thus, treating individuals at significantly lower risk than those currently being treated without using CRP screening was favored by these authors. However, if a normal CRP level meant that little or no benefit would result from statins, than strategy

b), treating the dual targets of LDL-C and CRP, would be the most cost-effective strategy. Notably, however, this analysis did in fact show that CRP testing is superior to current ATP III guidelines for individuals at "intermediate" FRS risk.

Other assumptions in this study were that statins remained inexpensive (generic simvastatin was used for their calculations), 17.5% of participants would discontinue statins within 6 months due to intolerance, rhabdomyolysis and renal failure would occur in 5–30 patients per 1 million treated with statins, and there were no long-term adverse effects of statins. If patient adherence to statin drugs was in fact poorer for any reason,[90] the calculations for cost-effectiveness would become invalid. In fact, the lead author of the paper remarked in a subsequent interview that "it doesn't take much to make statins not cost-effective for such large-scale use".

In their equal-effects scenario, it was assumed relative risk reductions from statins were not a function of FRS or CRP levels, and that statin therapy lowered the risk of MI by a factor of 0.77, and the risk of stroke by a factor of 0.83. In the differential scenario, it was assumed that individuals with high CRP values modified statin effectiveness, with relative risks of 0.46 for MI and 0.52 for stroke (data from JUPITER). An interactive presentation of the model with variable risk factors is accessible at http://med.stanford.edu/hsr/crp-screening.

The assumption of uniformity of effectiveness of all statins for all individuals, across ethnic and other groups, regardless of LDL-C, HDL-C, lipid subfractions, CRP and other biomarkers should be noted. If a normal CRP could exclude effectiveness of statins, then CRP-guided therapy would be best. According to the authors, because JUPITER did not have a normal LDL-C/normal CRP group for comparison, it remains unknown whether CRP elevations merely increases risk, or a normal CRP indicates ineffectiveness of statins in such a low/normal-CRP cohort. However, even though JUPITER did not have such an arm, data from other sources suggest that CRP does have discriminatory capability. In the AFCAPS/TexCAPS study, the relative risk reductions associated with the use of statins in patients with high CRP values was 42%, higher but not significant compared to the lower risk reductions in patients with normal CRP levels.[599] A subanalysis of JUPITER did demonstrate a relationship between outcomes in rosuvastatin-treated individuals and CRP levels.[279]

There was no consideration for any differential in efficacy, side effects, or potential interactions between rosuvastatin and simvastatin, but these potential differences may become important clinically. Simvastatin, as a highly lipophilic statin, is associated with a higher incidence of both myopathy and other adverse reactions than rosuvastatin, which is hydrophilic.[15] Further, since simvastatin is metabolized through the CYP3A4 enzyme, the probability of interactions with coadministered CYP3A4 substrates, inhibitors and inducers is much greater than with rosuvastatin, and package inserts by manufacturers reflect these data. For instance, simvastatin dosage is restricted when coadministered with with amiodarone and verapamil due to such interactions. Since polypharmacy is increasingly common, this may be a consideration in such a public health proposal.

In conclusion, if all the assumptions were true, then giving simvastatin 80 mg daily to all men who have no risk factors, without CRP testing, beginning at age 55, would be cost-effective, defined as less than $50,000 per quality-adjusted life-year (QALY). For men with one risk factor, eg, hypertension, simvastatin would be cost-effective beginning at age 50, and with 2 risk factors, at age 40. Data generated by this model provides some insight into possibilities in lieu of a large, costly, long-term clinical trial.[600]

Allocate statins using a risk-based, "tailored" strategy, rather than a standard or intensive ATP III treat-to-target approach

Five years ago Hayward et al[601] questioned whether treating to different LDL-C targets was actually evidence-based. These investigators reviewed controlled trials, cohort studies, and case-control studies that examined the relationship between lowering cholesterol levels and cardiovascular outcomes in patients with LDL-C < 3.36 mmol/L (<130 mg/dL). There was no support for the premise that the response of LDL-C to statins predicted the degree of cardiovascular risk reduction. It was concluded that patients with high risk should be treated with statins regardless of their initial LDL-C level.

Drawing from NHANES data (1977–1994), using the FRS, and employing a simulated model of population-level lifetime effects of 5 years of treatment with statin drugs, Hayward and coworkers[598] compared two treatment strategies. They chose either a conventional approach, using escalating treat-to-target NCEP-ATP III guidelines (in standard and more intensive options), or a risk-based approach (patients with 5%–15% CHD risk receiving 40 mg simvastatin daily, and those with >15% CHD risk receiving 40 mg atorvastatin daily). Participants were 30–70 years of age without a history of myocardial infarction. The investigators found that ≈70%

of patients would be treated similarly using the two strategies, 14% would be treated more aggressively using the risk-based approach, and 17% would receive more aggressive therapy following the treat-to-target protocol. Intensive treat-to-target treatment resulted in 15 million more people being treated and saved 570,000 more quality-adjusted life-years over the 5-year period. The tailored risk-based strategy resulted in just as many people being treated as intensive treat-to-target therapy, saved 520,000 more quality-adjusted life-years, but did not require as many patients to take high potency statins. More CHD events were prevented with the risk-based approach compared with the treat-to-target strategy, with rates of 62 and 15 per 1000 treated patients respectively. The treat-to-target strategy resulted in treatment of more patients with higher LDL-C levels, but with lower CHD risk, whereas the risk-based approach caused treatment of a greater number of patients with elevated CHD risk, but with lower LDL-C levels.

Using the risk-based approach incorporates the log-linear association between lowering LDL-C and CHD risk, which is maintained at lower values of LDL-C. The strategy also addresses the population-wide underutilization of statins in general.[602] In addition, the risk-based approach does not require monitoring of LDL-C, fewer physician encounters would be involved, and provides a simple prevention plan, eliminating guideline and treatment confusion among clinicians. Despite these advantages, and even if validated using a randomized trial, physician and patient acceptance would be difficult.

In countries where individualized care is not yet traditional and budgetary constraints are primary, a tailored population-based approach to achieve the most risk reduction will be well received. At each risk level, for cost-effectiveness, two people taking low-dose simvastatin provides better returns than one taking atorvastatin or rosuvastatin. Variations on this tailored treatment theme can be used to manage resources in optimizing population benefits with different statin schedules.[603,604] In actual practice with higher risk patients, the reduction in events may still be too low. Many cardiologists believe that limiting therapy to statins alone, the only class of agents for which significant evidence exists for hard-outcome efficacy,[605] will not result in lowering events by 50%, particularly using simvastatin.

Limitations in the use of surrogate biomarkers rather than patient outcomes in the treatment of dyslipidemia were discussed by Krumholz and Hayward.[606] Treating risk factors is a time-honored technique that has provided mechanistic understanding of the pathogenesis of atherothrombotic

disease, and is endorsed by the FDA. From a systems biology point of view, however, these authors observe that understanding mechanisms does not necessarily lead to improved patient outcomes. They note that a) statins lower risk of MACE, revascularization and stroke,[233,291] quite apart from the baseline lipid level; b) there is little or no evidence that combination therapy to achieve lipid targets actually improves patient outcomes; and c) the strategy used is more important than the change in cholesterol. To be sure, examples include the failures when torcetrapib, estrogen, clofibrate, and dextrothyroxine were used to lower cholesterol levels without reducing risk, and the absence of adequate evidence to support improvement in MACE associated with use of ezetimibe.

In the UK, because there are no data directly comparing high and low intensity statin therapy in primary prevention, treatment is conservative, using a "systematic rather than opportunistic" risk assessment, and simvastatin 40 mg is prescribed for individuals with a 10-year risk of 10%–20%. Titration to LDL-C targets and lipid and other monitoring is deemed unnecessary, and offering additional anti-lipid therapy is not routinely advised.[283,285,301,607]

With all proposals to lower cardiovascular risk, poor adherence is frequently the elephant in the room. As Rose[47] pointed out, a disadvantage of population- vs individual-based prevention is the small perceived benefit to the individual. When patients insist upon seeing objective improvement in their own risk factors as a requirement to continue taking simvastatin, adherence tends to wane.

Redefine the "normal" LDL-C level and eliminate multiple LDL-C goals

Defining normal LDL-C values based upon a Gaussian distribution in "asymptomatic" individuals repeats intrinsic errors because symptomatology is a poor index of either the activity or stage of atherosclerotic disease. The asymptomatic population is heterogeneous as far as cardiovascular risk, current pathology, and future events, and may not be "normal". The mean untreated adult LDL cholesterol value is $\approx$130 mg/dL ($\approx$3.4 mmol/L) in the USA, but lowering LDL-C levels to 100 mg/dL–130 mg/dL only prevents 25%–35% of events, with symptoms frequently dissociated from pathology. Evidence from contemporary hunter-gatherer societies and from wild primates suggests that humans are genetically better matched with "physiological" levels of LDL-C that may be on the order of 35 mg/dL–50 mg/dL.[608] Indeed, extrapolation of data from several meta-analyses indicate that in primary prevention, cardiovascular events would nearly be

eliminated at LDL-C < 60 mg/dL. In secondary prevention the corresponding threshold would be LDL-C < 30 mg/Dl.[607] Humans are distinguished by uniquely elevated LDL-C values compared with wild mammalian herbivores, carnivores, and omnivores. Convincing data indicate that the "Western" atherogenic diet is primarily responsible.[610,538]

Only a short time ago, the overriding concerns were basically: could such low LDL-C values be achieved; would it be safe to do so; and would sufficient clinical benefits be realized? The current tentative answers appear to be: yes; yes; and probably yes. Noting that answers to the last question must rest upon logical inference rather than hard evidence, Forrester[255] cites the >60% decrease in cardiac events associated with a lifetime of LDL-C lowering in *PCSK-9* hypofunction mutations to argue for prolonged statin therapy, and challenges the currently accepted "normals" for LDL-C levels. Further, a single "physiological" or putative normal LDL-C level – 50–70 mg/dL – could replace multiple targets presently assigned by global risk. Such an approach is supported by pathologic, epidemiologic and clinical trial data.[233]

The evidence that at very low levels of LDL-C cardiovascular events may approximate zero comes from several venues. First, comparative physiology of mammals and early human life indicate a genetic set-point for LDL-C that is less than half of the average untreated value in the Western world, ≈3.4 mmol/L (130 mg/dL). Feeding studies in many species of mammals vs those in the wild demonstrate a dose-related association of the Western diet with atherosclerosis. Near absence of atherosclerosis is associated with longevity and low LDL-C levels in contemporary hunter-gatherer societies.[610,611] When diets of such individuals are westernized, a rise in LDL-C and atherosclerosis progress hand-in-hand.[612] Extrapolation of event rates at progressively reduced LDL-C levels in primary and secondary prevention trials using statins implies that at very low levels, as mentioned above, events would virtually be eliminated.[608,609]

In a meta-analysis conducted by the Cholesterol Treatment Trialists' Collaboration,[233] a total of 170,000 high-risk participants in 26 randomized trials who began with an LDL-C of 1.8 mmol/L (70 mg/dL), were treated down to ≈1.3 mmol/L (50 mg/dL). With each 1 mmol/L reduction, the number of occlusive vascular events fell by about 20%, regardless of baseline LDL-C. However, despite the suggestion that stringent reduction of LDL-C could lower risk by about 40%–50%, reducing events across the board by 50% in the general population, especially with simvastatin, has yet to be demonstrated. In a large study of asymptomatic primary care patients with LDL-C < 130 mg/dL and CRP ≥ 2 mg/L,

those who who attained LDL-C < 50 mg/dL when treated with rosuvastatin 20 mg showed a striking 65% fall in the risk of cardiovascular events and a 46% reduction in total mortality.[344] Benefits were not associated with either the baseline LDL-C level or with a significant increase in adverse events. These data are consistent with the view that very low levels of LDL-C < 70 mg/dL may be achieved safely and produce greater improvements in outcomes than nonaggressive therapy. When indicated, lower appears to be better.

Setting a goal equal to the "physiologic" LDL-C in almost everyone has an immense advantage of simplicity. The ease with which this policy could be applied might raise adherence by practitioners and patients alike. However, this bold proposal is also accompanied by some uncertainties and caveats. Drawbacks related to toxicity, cost, and differences in potency may preclude achieving putatively physiological LDL-C levels in at least 25% of patients. Risk also varies according to variables other than LDL-C levels, including HDL-C, other triglyceride rich fractions, non-lipid risk factors, inflammation, enzyme activities, etc. Many individuals may resist preventive treatment, because they do not feel ill, with no discernible immediate physical benefit, added inconvenience and cost, and fear of side effects, which are widely disseminated on the internet. These factors may make adherence poorer than current levels, not better. The extent of adherence is probably of greater importance than the particular approach used.

It should be emphasized the notion that achieving an LDL-C of 50 mg/dL would lower cardiac events to negligible levels is theoretical, not proven. For example, many doubt that cardiovascular events would be eliminated in diabetics if LDL-C levels of 50 mg/dL – values observed in rats, cattle, and deer – were achieved. Such a prediction assumes that nearly 100% of CHD events may be explained by LDL-C elevation above that putative "physiological" value. In addition, present-day hunter-gatherer individuals experience a different life than those in developed civilizations, with a sizeable difference in exercise level, stress and pollutant exposure. Hence, while more intensive reduction in LDL-C will produce significant improvements in reducing cardiovascular events, only a partial, rather than total, amelioration will likely result from this proposal.

Follow treat-to-target lowering of LDL-C, but raise HDL-C

Keeping in mind that just ≈30% of cardiovascular events are prevented with statins, and even when maximally tolerated doses are used, only a further 16% can be suppressed, Drexel

et al[613] sought to identify the factors that were responsible for the residual risk in non-diabetic and diabetic patients. In a small study, vascular events were recorded over 5.6 years in 491 consecutive statin-treated patients with angiographically-proven stable CHD, amounting to 2750 patient-years. High values of triglycerides, small dense LDL, and low values of HDL-C and apoA-I predicted vascular events, but not LDL-C or apoB levels. In a small observational study, such results were only suggestive, but highlighted the potential importance of low HDL-C as a predictor of cardiovascular risk, especially in statin-treated patients. In a larger (n = 2910), community-based sample in the Framingham Heart Study, additional CHD risk associated with high TG or low HDL-C levels was only found in patients with insulin resistance.[630]

There has been considerable progress in understanding HDL metabolism, and interest in raising HDL-C levels as a means of reducing risk is keen. Larger ongoing clinical trials that target specific pathways in HDL metabolism may provide sufficiently robust data to support new treatment options. The present investigative focus includes increasing HDL-mediated reverse cholesterol transport, raising the proportion of more effective HDL subfractions, or producing functioning human apoA-I or surrogate molecules. Generally, there is only modest evidence showing that raising HDL-C, in addition to what is achieved by lifestyle modification alone, will improve outcomes.[358] Both the European[31] and Canadian[190] guidelines for dyslipidemia management emphasize that trial data do not show pharmacological treatment of HDL-C will lower cardiovascular risk. Indeed, recent reports using fibrates and niacin to lower risk have not changed this view.

Use a modified traditional approach which preserves LDL-C targets

Nambi and Ballantyne[227] proposed a formal protocol using the FRS, lifetime risk, and CRP, CIMT, CAC or genetic risk markers for further progressive refinement of stratification. After initially estimating FRS, if risk was >20%, the LDL-C goal would be 70 mg/dL. If FRS was low, or 0%–10%, lifetime risk would then be determined. For individuals with both a low 10-year and low lifetime risk, the prevailing NCEP-ATP protocol would apply. For those with a low 10-year risk, but a high lifetime risk, further stratification using CRP, CIMT, CAC score or genetic risk markers would be undertaken.

Finally, for those with an FRS of 10%–20% at intermediate risk, the current ATP III guidelines advise an LDL-C goal of <130 mg/dL and an optional goal of <100 mg/dL, which may change in ATP IV guidelines. These investigators also agree that the LDL-C value at birth, ≈50 mg/dL, may be

physiological, and cardiovascular benefits would be expected until those values are reached.

Give statins to low- and intermediate-risk individuals within a polypill

The polypill concept was proposed by Wald and Law[614] to lower LDL-C, blood pressure, serum homocysteine, and inhibit platelets regardless of pretreatment levels in a large segment of the population (over age 55), produce few side effects, with minimal expense. As safety of treatment rises and expense falls, risk stratification is considered less valuable. One-third of people taking this pill from age 55 were expected to benefit, adding an average of 11 years to life, free from a CHD event or stroke.[614]

In the Indian Polycap Study (TIPS), a polycap containing low doses of thiazide (12·5 mg), atenolol (50 mg), ramipril (5 mg), simvastatin (20 mg), and aspirin (100 mg) was studied in 2053 Indian subjects without cardiovascular disease, but with at least 1 risk factor[613] Based upon the results, there was a potential for a 62% reduction in relative risk in CHD and a 48% lowering of relative risk for stroke. This was short of the 80% risk reduction originally envisioned.[614,616] Not surprisingly, even though well-tolerated, acceptance and adherence was still a significant problem. A polypill feasibility study in Sri Lanka sponsored by WHO[617] found high patient acceptability, which need not have correlation with future adherence or outcomes. Compared to other techniques, the use of a polypill does not depend heavily upon personal responsibility for lifestyle change, since instructions are simple. Unfortunately, adherence to poor diets and inactivity is greater than adherence to polypills, and the protection afforded by the polypill, although impressive and with many advantages,[618–620] remains incomplete. Although it will go a long way in reducing cardiovascular risk, final long-term success in hard end points remains to be seen. The Use of a Multidrug Pill In Reducing cardiovascular Events (UMPIRE) study is beginning in the UK and in other venues, while other studies sponsored by WHO are in progress. In populated poor countries, the polypill may ultimately provide better protection than expensive, sophisticated care.

Conclusion

Alternatives for improving cardiovascular prevention based upon evolving concepts, new data, and revised goals have changed remarkably in recent years. In primary prevention, traditional risk factors used in combination to generate global scores do not predict risk well enough, nor do they discriminate sufficiently between those who will have cardiovascular events and those who will not. Chosing the best mix of approaches for

cardiovascular prevention cannot presently be based upon hard end point data, but partially upon an evidence-based synthesis using inductive reasoning. Even though the original belief that prevention was cost-ineffective has now been disproven,[621] at least for cardiovascular applications, there has been disappointing progress in effecting successful population-based primordial prevention. For truly effective improvements in cardiovascular risk, primordial prevention appears necessary as an adjunct to the high-risk strategy traditionally offered to individual patients. Wilkins and Lloyd-Jones[526] explicitly declare that the present paradigm of identifying high-risk individuals alone will never succeed in lowering the risk burden, even without considering further progression of obesity and diabetes.

The magnitude of the problem – pervasive poor cardiovascular health and its importance – has not been fully appreciated. Psychosocial aspects of behavior in embracing and adhering to primordial, primary, and secondary prevention are receiving greater attention.[85–87,622–626] According to one health belief model, negative health behavior is in part due to the widespread failure of people to accept disease preventives when disease is asymptomatic.[627] Part of the complex belief system involved leads to unrealistic optimism of vulnerability.[628] During assessment, the psychology and inaccuracy of patient perceptions of risk and the factors leading to physicians' underestimation of patients' risk are significant and incompletely understood.[170–173,198] As far as the estimation of cardiovascular risk burden is concerned, the chasm between perception and reality persists for both physicians and patients in North America, UK, and the EU. Given the lack of success and resistance to primordial prevention, population-wide pharmacological reduction of risk, previously rejected because of expense and potential side effects, is being reevaluated as a cost-effective maneuver. If one restricts evidence-based cardiovascular risk reduction to statins, the question reduces to what segment of the population will be eligible for how much of what statin or polypill.

Recent evidence suggests that attention to pediatric patients, at a time when habits are formed, and monitoring of adolescents as well as young adults, must increase.

The 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults,[32] a consensus of experts, reaffirmed a central role for global risk scoring in assessing risk in all adults. Similarly, a family history was recommended for all patients. While recognizing the large risk burden in asymptomatic adults, difficulty in identification of patients who ultimately suffer cardiovascular events, the significant number of patients who remain untreated and eventually succumb to CHD deaths,

this guideline set forth evidence-based recommendations for the identification and stratification of patients at risk.

Use of the Reynolds Risk Score, particularly in women, deserves consideration.[629] Lowering the threshold for risk level may bring more care to patients who will benefit. In the 2011 American Heart Association update to the guidelines for prevention of cardiovascular disease in women,[629] "high risk" among women is now defined as a 10-year CVD risk $\geq$ 10% rather than $\geq$20%.

Of all biomarkers, CRP is the best studied circulating biomarker, and provides information about activation of upstream cytokines driving inflammation. High levels of CRP are associated with endothelial dysfunction and predict future cardiovascular events. Use of C-reactive protein is recommended or accepted in guidelines for specific patients with intermediate risk.[15] Among imaging techniques, CIMT reflects intima-media thickening due to progression of atherosclerosis, refines risk assessment beyond global risk scores, improves predictability, and has been used successfully for serial re-evaluations. CAC documents the extent of calcification, a process which occurs later in the evolution of atherosclerosis. Patients with higher CAC scores generally have advanced, diffuse disease with accompanying noncalcified vulnerable lesions, accounting for its high prognostic value. Increasing appropriate use of CAC and CIMT, according to clinical circumstances, will refine risk evaluation, help guide treatment, and probably improve outcomes. Use of both CRP and CAC, since information provided involve orthogonal mechanisms, may offer unique advantages.[631,632] Recent work suggests that elevations in CRP levels predict a higher burden of coronary plaque, particularly mixed calcified arterial plaque, in asymptomatic individuals.[634] Rises in CRP concentrations appear to be associated with vulnerable plaque, drawing still more attention to the important role of inflammation in atherosclerosis.[635]

In patients with high risk, aggressive treatment to reduce risk factors should be instituted early and maintained for years. Since the incubation period and signs and symptoms of atherosclerosis span decades, randomized trials of a few years' duration provide little insight into outcomes of statin treatment over those 40–60 years. The most aggressive stance would include immediate treatment of patients with high- (FRS $\geq$ 20% or equivalent) or even intermediate-risk (FRS 10%–20%) with high potency statins. Rosuvastatin and high dose atorvastatin are drugs of choice, even if the baseline LDL-C is not elevated. Rosuvastatin produces the greatest reduction in LDL-C, LDL-P, and improvement in apoA-I/apoB with a favorable safety profile. Lowering current

LDL-C goals will undoubtedly enhance risk control and reduce event rates. However, even if all such patients received statins, cardiovascular events would still continue. The search for additional methods to lower residual risk, including using non-HDL-C as a target, raising functional HDL-C levels,[636] and mining LDL-C subfractions for clinically useful information, continues. The recent negative trials using torcetrapib, fibrates, and extended-release niacin are significant and collectively discouraging. This is particularly true concerning niacin in AIM-HIGH, in view of prior evidence supporting the use of this drug in a meta-analysis of 14 smaller trials[637] and ARBITER 6-HALTS. Nevertheless, the data reinforce the theme of this paper: intensive, unrelenting, lifestyle improvement and aggressive statin therapy are two pillars of management in the prevention of cardiovascular disease.

The enormity of pervasive poor cardiovascular health and its importance have not been fully appreciated and valued by the public, the media, health policy authorities, or legislators. Barring major unpalatable political changes, current trends in cardiovascular risk will undoubtedly continue. As such, there will be an even greater demand for pharmacological and invasive therapies. Most likely, success will be achieved through a combination of ongoing improvements in adherence, guideline compliance, novel treatments, and the valuable addition of primordial prevention in the form of programs such as the American Heart Association's Life's Simple 7™. Cooperation is essential, and each one of us – citizens, patients, biochemists, physicians, researchers, administrators, and public officials – have an essential role in supporting this common goal. Obstacles will be many, and the road hard and long, but recent advances now offer us greater and unique opportunities to meet the imposing challenge.

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Disclosure

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