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Screening Asymptomatic Subjects for Subclinical Atherosclerosis

Can We, Does It Matter, and Should We?

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Unheralded vaso-occlusive cardiovascular events (myocardial infarction, sudden death, and stroke) are common manifestations of atherothrombotic vascular disease, and accurate identification of individuals at risk of such events is highly desirable. Risk factor assessment and management have been the cornerstones of preventive strategies but are constrained by less than desirable accuracy and less than optimal compliance, respectively. In selected populations, noninvasive imaging using carotid ultrasound and/or coronary calcium score can incrementally refine risk assessment and may allow for improved adherence and better matching of preventive interventions to the magnitude of risk. Further refinements in the future may also be possible with novel biomarkers and measures of plaque phenotype. (J Am Coll Cardiol 2010;56:98–105) © 2010 by the American College of Cardiology Foundation

Burden of Cardiovascular Disease

Recently, I heard the famous author Dr. Deepak Chopra state on television: "We are all on death row; the only uncertainty is the length of reprieve and the method of execution" (1). As physicians, we strive to prolong life by delaying death and improving quality of life; any references to preventing death are obviously illusory because the only thing certain after birth is death. Atherosclerotic cardiovascular disease leading to coronary heart disease and stroke continue to be the leading causes of morbidity and mortality in much of the world (2). Cardiovascular disease accounts for nearly one-third of all deaths worldwide (17 million in 1999 and projected to be 25 million in 2020). In the U.S., cardiovascular disease and stroke cause 1 death every 33 to 37 s and cumulatively cause more annual deaths than cancer, respiratory disease, accidents, and diabetes combined (2). About 16 million Americans have coronary heart disease, and each year nearly 800,000 have a first acute myocardial infarction, 430,000 have a recurrent myocardial infarction, and nearly 800,000 have a first or recurrent stroke (2). Cardiovascular disease was estimated to have cost the U.S. health care system more than $400 billion in 2008. During the past several decades, we have witnessed significant gains against cardiovascular disease, with a significant decline in age-adjusted mortality; however, with the aging baby boomers and continually rising trends in obesity and metabolic syndrome/diabetes, we are likely to see a reversal of these gains within the coming decades with disastrous human and fiscal implications. Therefore, prevention of atherosclerotic cardiovascular events (myocardial infarction, sudden death, and stroke) remains a major imperative for health care professionals.

The process of atherosclerosis, now considered to be a chronic immunoinflammatory disease of medium- and large-sized arteries, often begins in childhood and adolescence and frequently remains clinically dormant until plaque rupture or plaque erosion leads to abrupt thrombosis triggering acute clinical events (3). In 2008, the sudden cardiac death of Tim Russert, a journalistic icon, brought focus on the value and limitations of current strategies for preventing unheralded cardiovascular events in asymptomatic subjects. Approximately 40% to 60% of major occlusive atherosclerotic cardiovascular events (myocardial infarction, sudden death) occur as the first manifestation (unheralded events), accounting for >700,000 such events annually in the U.S. (2). The identification of subjects at risk of such events is obviously important, if identification leads to implementation of and compliance with effective preventive measures that reduce such risk. Stress testing to detect a flow-limiting coronary stenosis among asymptomatic subjects is unlikely to identify a significant majority of at-risk individuals because nearly 70% of acute coronary events result from coronary lesions that are not hemodynamically significant or flow limiting before the event (4).

Framingham Risk Score (FRS) and Cardiovascular Events: Good but Not Good Enough

The Framingham study provided critical and extremely valuable information regarding risk factors associated with the development of atherosclerotic cardiovascular disease (5–7). The INTERHEART study demonstrated that nearly 90% to 95% of population-attributable risk of myocardial

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infarction is related to 9 potentially modifiable risk factors (smoking, apoprotein B/apoprotein A1 ratio, hypertension, diabetes, abdominal obesity, psychosocial factors, daily consumption of fruits and vegetables, regular alcohol intake, and regular physical activity) that apply to men and women, old and young, and in all regions of the world (8). Thus, risk factor inventory–based prediction models> using the FRS have been recommended as the cornerstone for risk stratification of asymptomatic subjects and matching intensity of preventive interventions (specifically, lipid-lowering drug therapy and cholesterol targets) to the magnitude of the predicted risk, as suggested by the National Cholesterol Education Program (NCEP) and the Adult Treatment Panel III (ATP III) (9,10). Assessment of a few readily available clinical and laboratory variables such as age, sex, total cholesterol level, high-density lipoprotein cholesterol level, smoking status, and systolic blood pressure are used to calculate a 10-year risk of cardiovascular events. According to the NCEP/ATP III guidelines, subjects are considered to be at low risk if the estimated 10-year event rate is <10%, at high risk if the 10-year event rate is >20%, and at intermediate risk if the 10-year event rate is between 10% and 20%. Based on this scheme of risk stratification, NCEP guidelines suggest cholesterol goals for each of the subsets (9,10). In 2003, the American College of Cardiology Bethesda Conference on Atherosclerosis Imaging suggested that low risk should be defined as a 10-year risk of ≤5% and intermediate risk defined as a 10-year risk of 6% to 20%. Although FRS and NCEP/ATP III guidelines are relatively simple, inexpensive, and useful, they are not good enough by themselves (11). Limitations of the FRS and NCEP/ATP III guidelines include a substantial underestimation of lifetime risk, especially in women when only a 10-year risk model is used, misclassification of high-risk subjects as low or intermediate risk, and misclassification of very low-risk subjects into higher strata of risk (11). Karim et al. (12) showed that in an ethnically diverse group of 498 asymptomatic men and women, 312 (63%) had a low FRS, and of these, 214 (69%) had noninvasive imaging evidence of subclinical atherosclerosis in ≥1 of the 3 vascular beds (coronary, aortic, and carotid). In the same study, of the 68 subjects with subclinical atherosclerosis in all 3 vascular beds, 35% had a low-risk FRS, 41% had an intermediate-risk FRS, and only 23% had a high-risk FRS (12). Furthermore, Akosah et al. (13) pointed out the shortcomings of the FRS in a study of 222 patients (men younger than 55 and women younger than 65 years of age) presenting with their first acute myocardial infarction over a 3-year period who were asymptomatic before the acute event. Based on their FRS, 75% of these patients would have been considered ineligible for statin use under the current NCEP guidelines that match intensity of treatment to the baseline FRS (13). A minority of patients with coronary heart disease have none of the traditional risk factors, but, more importantly, in a large proportion of patients with ≥1 risk factors, coronary heart disease does not develop (14). Furthermore, there is considerable variation in the severity of atherosclerotic burden at any given level of risk factor exposure, presumably attributable to additional known or unknown genetic and environmental risk factors and risk modifiers. The FRS also places a substantial number of women in the low-risk category using 10-year risk estimates even though they have a high lifetime risk; thus, very few women will reach the threshold for initiation of lipid-lowering or aspirin therapy (11,15). The FRS does not incorporate family history and many of the components of metabolic syndrome, both of which are important risk factors for coronary heart disease. A substantial number (>60% to 70%) of unheralded cardiovascular events occur in "low" and "intermediate" risk categories (16). Nasir et al. (17) showed that 79% of young men and women with significant coronary atherosclerotic burden displayed by coronary calcification were not eligible for pharmacotherapy based on current NCEP-ATP III guidelines. Although groups of patients can be placed in risk categories, many patients at risk would not be recommended for lipid-modifying therapy, and many patients in whom an event will not develop would be needlessly targeted for aggressive medical management (11). Thus, FRS and NCEP/ATP III guidelines, although reasonable for populations, remain suboptimal for individual subjects. In 2007, Ridker et al. (18) introduced the Reynolds Risk Score (RRS) for risk assessment in women, which, in addition to traditional risk factors, also incorporated high-sensitivity C-reactive protein (hsCRP) and family history of premature coronary artery disease. The RRS reclassified 30% of women estimated to be in the intermediate-risk group by the traditional FRS into a higher or lower risk category with improved accuracy. Subsequently, the RRS was tested in 10,724 initially healthy nondiabetic men age 50 years or older from the Physicians Heath Study who were followed for 10.8 years (19). The RRS was shown to be superior to the traditional FRS in predicting risk. Despite improved risk assessment with RRS compared with the traditional FRS, neither scheme is sufficiently accurate for individual risk assessment and, unlike the FRS, the RRS has not yet been fully validated outside the Women's Health Study and Physicians Health Study participants.

Abbreviations and Acronyms

CCS = coronary calcium score

CIMT = carotid artery intima-media thickness

CT = computed tomography

FRS = Framingham risk score

hsCRP = high-sensitivity C-reactive protein

NCEP = National Cholesterol Education Program

RRS = Reynolds Risk Score

Unconditional Treatment of All: Why Bother Screening for Risk? Why Not Treat Everyone?

Widespread application of preventive interventions (lifestyle, medications) without previous risk stratification (i.e., unconditional interventions for all) would be most appropriate if