Editorial

Risk Stratification for the Detection of Preclinical Coronary Artery Disease

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The cost of lost human value and dollars spent ($90 billion annually) due to coronary disease in our society is of great concern and is reason for increased efforts to prevent coronary artery disease and its consequences.1 The reduction in mortality, acute coronary event rate, and need for coronary revascularization attributable to lipid lowering with HMG-CoA reductase inhibitors in the recent primary coronary prevention trials has therefore been encouraging.2,3 These studies have prompted many physicians and primary coronary prevention trials has therefore been encouraging with HMG-CoA reductase inhibitors in the recent need for coronary revascularization attributable to lipid lowering.

Cardiovascular disease (CHD), are not cost-effective in asymptomatic individuals who are most likely to benefit from risk-reduction therapy. However, classic risk models that use the Framingham or MRFIT (Multiple Risk Factor Intervention Trial) studies suffer several flaws, in particular the inability to incorporate new risk factors (eg, homocysteine) and the impact of diet, estrogens, personality traits, and physical activity. The ATP II guidelines are based on risk modeling.4 Using age, sex, LDL cholesterol of 190 mg/dL or 160 mg/dL with ≥2 risk factors, ≈15% of US men and women aged 35 to 74 years are characterized as high risk and eligible for drug treatment.6 The 15% deemed high risk represent ≈45% of likely coronary deaths, with a specificity of 86%.6 The receiver operating characteristics (ROC) curve (sensitivity versus 1-specificity) for the ATP II guidelines to predict coronary deaths is 0.74, a value considerably better than noninvasive testing for ischemia in asymptomatic individuals.

When patients are selected by the ATP II guidelines, coronary prevention compares favorably with other healthcare costs in dollars per quality-of-life-year saved ($25 000 to $35 000), but if less rigorous criteria were used to select persons for treatment, the cost in the United States could be staggering. The annual cost of statin therapy is ≈$1000 per patient. From the West of Scotland Coronary Prevention Study, it is estimated that treating 1000 hypercholesterolemic middle-aged men with a statin for 5 years will prevent 20 nonfatal MIs, 7 coronary and 2 noncoronary deaths, 14 coronary arteriograms, and 8 revascularization procedures.2 The converse is that >950 persons have been treated without a clear benefit. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), after 5 years of treatment with lovastatin, middle-aged and elderly men and women with average coronary risk and lipids (HDL <50 mg/dL) had a 37% reduction in acute coronary events compared with a group treated with a placebo.3 The event rate in lovastatin-treated subjects averaged 7 per 1000 patient-years compared with 11 per 1000 patient-years in the placebo group, an annual incidence of 0.8% and 1.36% events, respectively. Treatment of 1000 men and women with lova-

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One early approach to risk stratification was exercise testing, first with the ECG and more recently with radionuclides and echocardiography. These tools, although useful in the evaluation of patients with symptoms or known coronary disease (CHD), are not cost-effective in asymptomatic individuals with or without coronary risk factors. The realization that the majority of acute ischemic events occur from rupture of hemodynamically insignificant coronary artery lesions explains the low predictive value of these tests for identifying asymptomatic persons who will sustain an MI or coronary death, why they are often misleading, and why they no longer are an appropriate part of the "executive physical."

Risk modeling based on epidemiological studies is another method of estimating the probability of death or MI in an individual. The goal of risk assessment is to identify persons at highest risk of a future event or at a given threshold. The information allows for appropriate selection of individuals who are most likely to benefit from risk-reduction therapy. However, classic risk models that use the Framingham or MRFIT (Multiple Risk Factor Intervention Trial) studies suffer several flaws, in particular the inability to incorporate new risk factors (eg, homocysteine) and the impact of diet, estrogens, personality traits, and physical activity. The ATP II guidelines are based on risk modeling.4 Using age, sex, LDL cholesterol of 190 mg/dL or 160 mg/dL with ≥2 risk factors, ≈15% of US men and women aged 35 to 74 years are characterized as high risk and eligible for drug treatment.6 The 15% deemed high risk represent ≈45% of likely coronary deaths, with a specificity of 86%.6 The receiver operating characteristics (ROC) curve (sensitivity versus 1-specificity) for the ATP II guidelines to predict coronary deaths is 0.74, a value considerably better than noninvasive testing for ischemia in asymptomatic individuals.

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statin for 5 years would be expected to prevent 12 MIs, 7 bouts of unstable angina, and 17 coronary revascularizations.

The cost to treat the 26 million people characterized as high risk by ATP II is estimated at $26 billion.1 Extending the treatment guidelines to the APCAPS/TextCAPS study criteria would require treating >50% of the adult population, with an estimated discounted cost of $50 billion. Of course, the major concern to the healthcare purchaser (particularly governments) is that even if the cost of drugs is reduced and investment in coronary prevention is “worth it” compared with other societal issues, costs will continue to rise as coronary events are simply delayed.

Although the guidelines are reasonably effective at discriminating persons at high risk destined to have an event, it is of no small concern to physicians and educated individuals that more than half the coronary deaths and the majority of MIs in the United States occur in persons characterized as low or intermediate risk.6,7 It is for these reasons the promise of characterizing coronary risk by the detection of coronary calcification by electron-beam CT (EBCT) is attractive to physicians and apprehensive consumers willing to pay $400 to $500 for a 15-minute examination that does not require undressing or special preparation. Furthermore, if the absence of coronary calcification in middle-aged men and women characterized a population with negligible risk for future coronary events, drug treatment could be avoided or delayed, an attractive hypothesis to patients and payers.

The comprehensive American Heart Association (AHA) statement on coronary calcification concluded that although there are sufficient data to suggest that evaluation with EBCT is ready for clinical application in patients with chest pain, there are insufficient data to conclude whether the relation between coronary calcium and coronary risk warrants the use of calcium screening in low-risk asymptomatic subjects.8 Arad et al9 reported that at 19 months after an EBCT, asymptomatic subjects with a calcium score (CAC) >100 and >160 had ORs of 20:1 and 35:1 for coronary events, respectively. Because subjects paid for the procedure, enrollment by physicians or through self-referral, and coronary events included revascularization and were not independently verified, this study was not considered definitive.8

Detrano et al10 report in this issue of Circulation that screening asymptomatic high-risk subjects for coronary calcification with EBCT does not effectively identify those who will have coronary events within 3.5 years. With ROC curves used to express accuracy for predicting death and nonfatal infarction, the calcium score (ROC 0.64±0.05) did not improve on the Framingham risk profile (ROC 0.69±0.05), and the presence of calcium did not add to the relatively weak predictive value of risk models. These findings are counterintuitive on the basis of previous observations. Namely, there is consistent evidence that coronary calcification correlates highly with the presence and degree of obstructive and nonobstructive atheromatous plaque at autopsy11 and by intravascular ultrasound,12 the presence of obstructive disease by angiography,13 and nonfatal infarction and need for subsequent coronary revascularization in both asymptomatic individuals8,14 and persons undergoing coronary arteriography.15

Does the South Bay Heart Watch study support a conclusion that screening asymptomatic persons at risk is inappropriate and that the results in the 1173 patient-pay Arad study should be ignored because of treatment or decision bias based on calcium scores? Unfortunately, the South Bay Heart Watch study suffers similar limitations. The 1196 volunteer subjects with a risk of 3.3±3.6% for fatal and nonfatal coronary events according to the Framingham model were predominantly elderly men with a mean age of 66±8 years. They were drawn from the 1461 South Bay Heart Watch subjects from whom the authors concluded the number of vessels with coronary calcification detected by digital subtraction cardiac fluoroscopy was an independent predictor of death or infarction.16 The probability of both selection and treatment biases resulting in a decrease in the predictive value of EBCT and the Framingham model is high. Of the original cohort, >10% were excluded from the EBCT study because of death (percent cardiac not reported), angina, or acute MI occurring within 30 months and typify a group identifiable by coronary calcification.9,11,12,14,15 Subjects were initially recruited knowing they were high risk and were informed of the results of the initial cardiac fluoroscopy and subsequent EBCT. It is highly likely that many consulted physicians and were recommended diet, aspirin, and an HMG-CoA reductase inhibitor. The knowledge of calcium on EBCT in self-referred subjects is known to positively influence behavior,17 and it is unlikely a “high-risk” volunteer study population would respond differently. Finally, that EBCT failed to predict coronary events better than a risk model in a high-risk older population cannot be extrapolated to the general population at risk for coronary events. Despite these shortcomings, it seems reasonable to conclude that the use of routine EBCT to risk-stratify asymptomatic patients for future risk of ischemic events is not currently justified on a clinical basis, pending data from future well-designed, prospective clinical research studies to the contrary.

The failure of EBCT to add to the assessment of the risk of MI and death in asymptomatic personsas reported by Detrano et al10 should not detract from future efforts. Advances in our understanding of the pathophysiology of coronary disease and plaque rupture hold great promise for improving risk stratification. Inflammatory markers such as C-reactive protein and interleukin-6 may be helpful for predicting the risk of ischemic events in established CHD and asymptomatic individuals. Further insights into the importance of various atherogenic lipoproteins and DNA polymorphisms, antioxidant balance, circulating heat shock proteins, and thrombosis/fibrinolysis balance are necessary. It is likely in the future we will create risk models based on lifestyle, biochemical markers, and genetic susceptibility, possibly in combination with selective use of imaging modalities including EBCT, B-mode ultrasonography for measuring carotid wall thickness and endothelial function, and MR detection of plaque structure. The NHLBI subclinical coronary artery disease study of 18 000 men and women testing the utility of many of these tools will be completed in about 2010.

Until the scientific evidence justifies a change in strategy, the physician community can do the most good by spending
more time educating, risk-stratifying by standard guidelines, and supplementing with clinical judgment. As a profession, we should be vigilant that in our quest and enthusiasm to prevent MI and sudden death we do not “get ahead of the curve” in our application of new knowledge that has such important public health implications. The role of the cardiologist should be to insist that any advice given in regard to coronary risk stratification or modification be based on well-designed epidemiological studies and prospective randomized clinical trials and that any incremental costs be consistent with the best interests of society.

References


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