

Atherosclerotic Risk Factors Revisited

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Risk factors have traditionally been used to define the statistical likelihood of the development of clinical coronary artery disease in populations of asymptomatic patients; they provide no direct information regarding the actual presence or degree of disease in patients at a given point in time. Therefore, the correctness of the decision to initiate or withhold drug therapy based on risk factors alone is derived from probability rather than direct demonstration of the subclinical atherosclerosis that provides the framework for the clinical manifestations.

CHALLENGES TO CONVENTIONAL RISK ASSESSMENT

The dangers of this approach are highlighted by the work of Akosah et al,¹ who showed that 75% of previously asymptomatic younger adults (men <55 and women <65 years of age) presenting with a myocardial infarction would not have been started on a statin before the event according to the Framingham risk score-based National Cholesterol Education Program Adult Treatment Panel III guidelines.² Half of the highest risk group (>20% 10-year risk) and 44% of the intermediate risk group (10% to 20% 10-year risk) would not have been started on drug therapy. The percentages were far worse in the 2 lowest risk categories; that is, no statin would have been prescribed for 84% of those who had a myocardial infarction and 0 to 1 risk factors in whom a Framingham risk score need not be calculated by National Cholesterol Education Program guidelines, and for 94% of the 1% to 10% Framingham 10-year risk group. These 2 lowest risk groups comprised 50% and 20% of the total group, respectively!

The concept that the arbitrary parameters of low-density lipoprotein (LDL) cholesterol used to calculate the Framingham risk score define those patients who will benefit from statin therapy has been firmly rejected by the Heart Protection Study.³ In this landmark trial, patients with LDL cholesterol <100 mg/dl achieved the same approximate 25% benefit from simvastatin therapy as those with higher levels, and the investigators concluded "The size of the benefit depends chiefly on individual's overall risk of major vascular events, rather than on their blood lipid concentrations alone."

ALTERNATIVE RISK ASSESSMENT

Patients with established vascular disease are, by definition, at high risk and require statin therapy irre-

spective of LDL cholesterol level. However, in the primary prevention population, in whom conventional risk assessment by the Framingham risk score is problematic, how should treatment decisions be implemented? Three recent studies have provided the strongest arguments to date for the use of calcified plaque determined by electron beam tomography (EBT).

Kondos et al,⁴ in 5,635 asymptomatic low- to intermediate-risk patients followed for 37 ± 12 months, found that the presence of any coronary artery calcium (CAC) by EBT was associated with a relative risk for events of 10.5, compared with 1.98 and 1.4 for diabetes and smoking, respectively. In women, only CAC was linked to events, with a relative risk of 2.6; risk factors were not related. The presence of CAC provided prognostic information incremental to age and other risk factors.

The second study, by Shaw et al,⁵ followed 10,377 asymptomatic patients for 5 years after the EBT evaluation. All-cause mortality increased proportional to CAC, which was an independent predictor of risk after adjusting for all of the Framingham risk factors ($p < 0.001$). Superiority of CAC to conventional Framingham risk factor assessment was demonstrated by a significantly greater area under the receiver-operating characteristic curves (0.73 vs 0.67, $p < 0.001$). An incremental value of CAC to Framingham risk was also established by a significant increase of the area under the receiver-operating characteristic curves (from 0.72 for Framingham risk to 0.78 with the addition of CAC [$p < 0.001$]).

The third study, by Arad et al,⁶ presented in the Late Breaking Clinical Trials session at the 2003 American College of Cardiology national meeting, addressed the most common criticisms of EBT prognostic papers. Rather than being a retrospective analysis of self-referred patients with the possible implicit selection bias, it was a prospective, population-based study of 5,585 asymptomatic men and women. The results remarkably mirrored previous studies. Raggi et al⁷ reported an annual event rate of 0.11%/year associated with a zero calcium score in 792 retrospectively evaluated patients. In the prospective study by Arad et al,⁶ the corresponding event rate was 0.12%/year. Patients with higher scores had progressively higher event rates, and scores >100 were associated with relative risks from 12 to 32 and event rates >2%/year. Of great importance from the epidemiologic perspective was that CAC fulfilled the requirement of being independent of and incremental to the existing gold standard, the Framingham risk score. The areas under the receiver-operating characteristic curves were 0.81 for CAC and 0.71 for Framingham ($p < 0.01$). Moreover, classification by CAC tertiles changed approximately 67% of patients classified as intermediate risk

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by Framingham (1% to 2%/year event rate) to either low or high risk as determined by actual outcome. In the Framingham high-risk category (>2%/year event rate), 45% were correctly moved to lower-risk categories by CAC tertile reclassification. Finally, in the Framingham low-risk group (<1%/year risk), 29% had scores >100 with an associated 1.7%/year event rate.

Therefore, it appears appropriate to use the presence or absence and the amount of CAC as the most powerful arbiter of risk, particularly—from the broad public health perspective—in the intermediate-risk population. This recommendation is contained in the final report of the National Cholesterol Education Program guidelines⁸: “Therefore, measurement of coronary calcium is an option for advanced risk assessment in appropriately selected persons. In persons with multiple risk factors, high coronary calcium scores (e.g., >75th percentile for age and sex) denotes advanced coronary atherosclerosis and provides a rationale for intensified LDL-lowering therapy. Moreover, measurement of coronary calcium is promising for older persons in whom the traditional risk factors lose some of their predictive power.” In recognition of the limitations of age in predicting risk, Grundy⁹ has recommended that “calcium scores are best used. . . by replacing age as a risk factor in Framingham risk equations—they are a better measure of coronary plaque burden.”

The general consensus may still be that Framingham high-risk patients should be treated and low-risk patients should not, irrespective of the calcium score as suggested by the editorial response¹⁰ to the Kondos et al report.⁴ Arguments could be made to the contrary based on the previously mentioned studies, particularly the Akosah et al¹ report documenting the dismal prediction of risk in the lowest risk categories.

The impact of EBT on outcomes has not yet been determined, but, as the editorial by Weintraub¹⁰ concedes, it “would require a massive clinical trial, which is extremely unlikely to ever be mounted.”¹⁰ This same lack of outcome data applies to the use of echocardiography and to all forms of stress testing. Simply stated, there are no randomized studies demonstrating improved outcomes in patients who underwent echocardiography or stress tests compared with a matched group of patients who did not. Yet, the 2 technologies, by virtue of their power to demonstrate basic and critical information regarding cardiac function and perfusion, are accepted without question. The addition of the studies by Kondos et al,⁴ Shaw et al,⁵ and Arad et al⁶ to the prior extensive supporting data has provided the critical mass of evidence establishing CAC as the most potent predictor of risk, justifying the incorporation of CAC into the routine armamentarium.

The public health implications are staggering. Several reports demonstrate, both in older and younger populations of previously asymptomatic subjects, that CAC is present in 95% of patients experiencing events.^{3,11,12} By extrapolation, CAC could identify the pool of high-risk patients out of which 95% of the

650,000 Americans presenting each year with a myocardial infarction or sudden death as their first symptom¹³ will emerge. Events can be decreased by 24% to 37% with statin monotherapy^{14–17} and perhaps considerably higher with combination therapy and aggressive risk factor modification.¹⁸

ATHEROSCLEROTIC RISK FACTORS REVISITED

This then leads to the title of this editorial: “Atherosclerotic Risk Factors Revisited.” The value of risk factors may reside more in determining the targets of intensive therapy in those with increased risk, rather than in factoring them into an equation that performs suboptimally in determining that risk. Once risk is established, either by clinical disease in secondary prevention or by CAC-defined subclinical disease in primary prevention, aggressive attention should be directed to modifying those factors that are modifiable. For instance, age, sex, and family history of premature coronary disease are clearly non-negotiable. Cessation of tobacco usage and strict control of diabetes and hypertension are a given. The lipid arena is more open to interpretation. National Cholesterol Education Program primary prevention guidelines call for the institution of statin therapy for LDL cholesterol reduction according to the Framingham risk score estimate.² A more reasonable approach may be to institute statin therapy for patients of above-average risk by CAC, irrespective of their baseline lipid level, and, as implied by the Heart Protection Study,³ even for patients with LDL cholesterol <100 mg/dl. The CAC cut-off points for initiating therapy may be a score >100 as suggested by the St. Francis Heart Study,⁶ or an amount that is either >75% of that noted in persons of the same age or sex as suggested by the National Cholesterol Education Program Adult Treatment Panel III final report⁸ or >50%, which Raggi et al¹⁹ found to be associated with >2%/year event rate. The American Heart Association Prevention V Update²⁰ used a score >80 to implement aggressive drug treatment in Framingham intermediate-risk patients. With a zero score, they concluded that “one would not be justified to intervene with costly lipid lowering or blood pressure lowering drugs at this time.”

The National Cholesterol Education Program guidelines suggest getting patients to their LDL goal before addressing non-LDL abnormalities, such as HDL cholesterol and triglycerides. They also introduce the emerging risk factors of lipoprotein(a) and small, dense LDL but do not discuss or recommend specific therapy for these disorders. Because LDL-directed statin monotherapy in many trials has resulted in risk reduction in the 24% to 37% range compared with placebo,^{13–16} and the Veterans Affairs High-density lipoprotein cholesterol Intervention Trial (VA-HIT) yielded a 24% event reduction after fibrate treatment of HDL and triglycerides,²¹ strong consideration should be given to combination therapy to treat LDL and HDL cholesterol and triglycerides from the onset of treatment, without waiting to first achieve LDL cholesterol reduction. The desired outcome would be

an additive decrease in events with combination therapy, the feasibility of which is demonstrated by the 89% event reduction in the HDL-Atherosclerosis Treatment Study (HATS) with the combined use of simvastatin and niacin.¹⁸ Because niacin reduces lipoprotein(a) and increases LDL and HDL particle size, routine identification and treatment of these disorders should be considered.

The absence of significant plaque does not imply that modifiable risk factors should be ignored. On the contrary, they should be aggressively targeted by the diet, exercise, and weight-loss oriented therapeutic life changes arm of the National Cholesterol Education Program guidelines.² Aggressive prevention is always the rule. However, the use of pharmacology, as suggested by the American Heart Association Prevention V Update,²⁰ may be better reserved for those of sufficient risk to warrant this intervention.

CONCLUSION

The most important role of risk factors may be to identify the modifiable targets of risk reduction in patients with risk already established by clinical events or significant CAC. Their use in defining the risk itself is problematic. Framingham risk scores may be used to loosely stratify the low-, intermediate-, and high-risk primary prevention subsets, but, particularly in the intermediate-risk group, they should not be the arbiter of therapy. In view of recently presented large prognostic studies,^{4–6} this role is better reserved for EBT-determined calcified plaque burden.

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