EDITORIAL COMMENT

The Prudent Person’s Paradox*

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We can all name a number of people—friends, family, and patients among them—who, despite conscientious effort on their part and the achievement of what for all intents and purposes appears to be a “normal” risk factor profile, experience an acute coronary event. The “Prudent Person’s Paradox,” if you will, is a sort of antithesis of the “French Paradox,” where, despite what appears to be a predisposing diet and lifestyle, the French maintain(ed) a lower than expected incidence of coronary heart disease (CHD) (1).

In this issue of the Journal, the paper by Akosah et al. (2) regarding the ability of the new National Cholesterol Education Program guidelines (3) to identify people needing aggressive coronary risk factor intervention, provides elaborate documentation of this phenomenon. The authors found that even though the new guidelines essentially “widen the net” for those who should receive greater attention to risks, they still underestimate the risk of acute coronary events in “young adults” (men ≤55 years of age and women ≥65 years of age). For example, as many as 58% had low-density lipoprotein cholesterol levels ≤130 mg/dl and 50% did not have multiple risk factors. Only 25% of the men and 18% of the women were appropriately identified for lipid-lowering pharmaotherapy. Similarly, among the subjects with moderate risk (10% to 20%), only half were treatment-eligible. Of the subjects, 70% actually fell into the lowest two risk categories. More people qualified for pharmacologic intervention in the lowest risk category (8% of subjects) than in the third quartile (1% of subjects with 2+ risk factors, <10% risk). Why, despite all the time and earnest effort expended for their revision, do such guidelines still seem so off the mark? Earnest practitioners want to know: does risk factor scoring translate into clinically relevant decision making?

Problems with accuracy of risk estimation. Biologic variation in risk factors affects the accuracy of correct categorization of patients in primary prevention screening. Reynolds et al. (4) showed that at internationally recommended 10-year CHD risk treatment threshold levels of 15%, 20%, and 30%, the 95% confidence intervals were: ±5.1%, ±6.0%, and ±6.9% for single-point; ±3.6%, ±4.2%, and ±4.9% for duplicate-point; and ±2.8%, ±3.3%, and ±3.9% for triplicate estimates, respectively. Consequently, using the 30% risk threshold with single-point estimation, 30% of patients who should receive treatment would be denied it and 20% would receive treatment unnecessarily, figures very consistent with the observations of Akosah et al. (2). “Multiple measurements improve precision but cannot absolutely define risk,” conclude Reynolds et al. (4). This study suggests that biologic variation in cardiovascular risk factors has profound consequences on calculated risk for therapeutic decision making and probably contributes to the inaccuracy of risk estimation.

Imprecise measurement of risk factors causes misclassification of individuals, limits sensitivity to detect those with true high risk, and dilutes associations between risk factors and disease (5). For cholesterol and CHD (a linear relationship), uncorrected estimates tended to exaggerate the effectiveness of “high-risk” strategies relative to the “population-based” approach.

Haq et al. (6) found that methods based on cholesterol threshold and counting of risk factors to be too inaccurate for targeting drug therapy for primary prevention of CHD. They compared the accuracy of several CHD risk assessment methods and found that cholesterol threshold (≥6.5 mmol/l) plus two risk factors had a sensitivity of 59% and specificity of 63% and, thus, misidentified some very high- and low-risk patients. Framingham-based methods using total cholesterol alone had a sensitivity of 90% to 98% and specificity 37% to 43%, identifying high-risk patients well, but inappropriately identifying some at very low risk. Methods based on total cholesterol:high-density lipoprotein cholesterol ratio had a sensitivity of 90% to 98% and specificity 60% to 63%, and did not incorrectly identify people at very low CHD risk.

The right questions . . . the right answers. There’s an old adage that you will not get the right answers if you are asking the wrong questions. Frankly, it seems practitioners tend to apply diagnostic tests for coronary disease in their historical context, rather than how they fit currently into the most up-to-date understanding of the coronary disease continuum. What is it that you want to know? Is it if someone has a disease that is advanced to the point where revascularization should be considered? Or, are they at near-term risk of plaque rupture? For the appropriate initiation of medical therapy, we need to know if there is any disease present, not 50% obstruction, an arbitrary definition of CHD, or even 65% obstruction when compromised perfusion during stress can be documented. By the time people experience their first coronary event, the disease is, in fact, fairly advanced and the likelihood of something untoward occurring is great (7). We should be thinking more of identifying who is the vulnerable patient rather than who has the vulnerable plaque (8).

If you want to answer the question of whether someone has any evidence of the disease, then subclinical diagnostic modalities are required. Such surrogate markers are now

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available and are being further investigated to identify disease in its early phases in an attempt to decrease cardiovascular morbidity and mortality. Coronary artery calcification is a useful surrogate marker of coronary artery disease, and it can be visualized and measured noninvasively by means of electron beam tomography (EBT) imaging (9). This is an especially challenging issue for the early identification of at-risk women. Assuming a higher risk in subjects with EBT-defined subclinical CHD than in those without, only 58.6% of a female cohort of subjects would be correctly identified by NCEP guidelines as either higher or lower risk, with correct identification of 65.5% of the younger and 52.2% of the older women (10). Such studies demonstrate the shortcomings of employing guidelines to identify asymptomatic women with subclinical CHD, particularly women older than 55 years, and suggest the need for validation and increased application of subclinical markers for primary prevention in the female population. Risk scoring systems will always perform best for assessing populations, but will predictably fall short if relied on for individual patient management decisions.

If you want to know who may be a candidate for an impending acute coronary event, then clearly the application of newer risk markers such as high sensitivity C-reactive protein will be the tools of choice (11), in addition to playing an important role as an adjunct for global risk assessment in the primary prevention of cardiovascular disease (12), and for identifying individuals with normal lipid levels who are at increased risk for future coronary events (13). In time, other emerging technologies will likely be available (14,15).

Precluding the prudent person’s paradox. As advocates for the public and our patients, we need to apply both a population strategy and a clinical strategy (16). Determination of risk scores will help us identify the vulnerable patient who needs aggressive management of modifiable risks, even if it does not necessarily identify the patient’s precise location on the coronary continuum (17). This applies equally to those who are thought to be low-to-moderate-risk based upon lipid profile or multifactorial risk assessment (18,19). In addition, the careful application of novel complementary diagnostic technologies will provide relief to those who are candidates for the inevitable disappointment of the prudent person’s paradox.

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