Nontraditional Markers of Cardiovascular Disease Risk Can Improve the 2013 American College of Cardiology/American Heart Association Prevention Guidelines: Insights From the Multi-Ethnic Study of Atherosclerosis Investigation

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The ability to accurately identify individuals at increased risk for a cardiovascular (CV) event is critical to efficient heart disease and stroke prevention. Since the publication of the results of the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) in 1984 attempts to establish guidelines useful in the identification of patients who would receive the most primary cardiovascular disease (CVD) prevention benefit from blood cholesterol reduction, has been debated.1 Recently, the debate has expanded to suggest that the reduction of the atherosclerotic CVD risk threshold from the American College of Cardiology/American Heart Association (ACC/AHA) 2013 from 7.5% to a lower 3.0% would reduce CVD events even further and be cost-effective.2,3 Population-wide recommendations make public health sense but fail to address the heterogeneity of this disease and the need to personalize both diagnosis and treatment. The concept that 1 set of guidelines is best for all individuals is woefully outdated in the current age of sophisticated metabolomics and genetics.

We know that the majority of events occur in people who do not exhibit classic elevations in low-density lipoprotein cholesterol (LDL-C), so it makes some sense to expand the catchment area with a broad approach.4 This well-intentioned broad approach to heart disease prevention relies on the estimated probability of disease development, which, in turn, is based on a population-based statistical relationship that must then be extrapolated to the individual patient seen by the clinician. Such an approach casts a wide net that indeed identifies some individuals who proceed to incur a CVD event and deserve therapy in addition to a statin drug in an individual patient. Yet, many events occur in populations defined as low risk by the public health approach. Second, is noninvasive imaging evidence of disease useful? Third, a public health approach ignores the complex heterogeneity of this disease and recent advances in metabolic and genetic factors, including individual differences in response to statins based on genetic heterogeneity.7

Many Events Occur in Populations Defined as Low Risk

Yeboah and colleagues report that in their MESA cohort 81% of subjects not taking a statin had a calibrated Pooled Cohort

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Equation <7.5% and over 10 years 57% of 320 atherosclerotic CVD events occurred in these low-risk subjects. This is similar to the previous attempts to use LDL-C cut points to define risk and treatment recommendations. In multiple clinical trials patients continue to have events despite LDL-C reduction. For example, even in the low LDL-C Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial in which the median baseline LDL-C was 109 mg/dL and 55 mg/dL with treatment, 251 (2.8%) of placebo patients experienced a primary CVD event and 142 (1.6%) of statin-treated patients also experienced an event. The danger for our patients in threshold treatment guidelines is that many individuals in the reputedly low-risk group go on to experience a CVD event. This suggests that other factors are present and contributing to the disease, and statin treatment alone leaves many individuals still at risk.

Is Noninvasive Imaging Evidence of Disease Useful in Addition to the ACC/AHA 2013 Guidelines?

The clinical utility of noninvasive imaging has received considerable discussion. Yeboah and colleagues contribute to this discussion with the report that 6.8% of subjects with a calibrated Pooled Cohort Equation 10-year risk <7.5% had a CAC score >300 Agatston units and also had the lowest NNS (14.7) to become statin eligible and a relative risk of 4.0. The mean age of the subjects was 61 years, which suggests that negative or low CAC scores were not confounded by low age. The measure with the second lowest NNS was a family history (no age cutoff) with a NNS of 21.8 and the highest relative risk of 4.3. The simple addition of family history to risk classification and CAC scoring appears not to be specific to a single Agatston score range (Figure). Patel and colleagues have shown that Agatston scores <400 may still be relevant in subjects with a family history of premature CAD. On the low end of the CAC score spectrum, the recent Framingham analysis examined CAC scores and confirmed a score of 0 was associated with a low CVD rate of 1.6%. This suggests that CAC testing may have clinical utility and be cost-effective on an individual basis. An informal review of CAC testing costs among cardiovascular colleagues and their institutions has revealed that the cost to the patient for a CAC test and Agatston classification ranges between $50 and $350 with an average cost of $99. At a price of $99, the cost is similar to dinner for 2 in a metropolitan city. Second in line for a low NNS was the simple addition of family history (no age cutoff). There is essentially no cost to this measurement.

A Public Health Approach Ignores the Complex Heterogeneity of This Disease and Recent Advances in Metabolic and Genetic Factors

Factors that go beyond LDL-C contribute to CHD and are not accounted for in the ACC/AHA 2013 guidelines. Some are relatively common such as elevated lipoprotein(a), disorders of lipoprotein heterogeneity, amino acid disorders, genetics, and subtle yet relevant disorders of thrombosis and inflammation. Large population analyses, as have been recently reported, have failed to incorporate these parameters in their analysis, which does not mean that they lack importance or relevance.

Thus, we are left with the challenge of a public health population-wide approach versus a personalized approach that may involve relatively recent noninvasive imaging, metabolic, and genetic tools. The cost to the patient of these modern tools continues to decline and places the findings of Yeboah and colleagues in perspective. Yeboah and colleagues demonstrated that inclusion of nontraditional measures of atherosclerosis risk can improve the personalization of the ACC/AHA 2013 guidelines.

Disclosures

None.

References


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