Statins, risk assessment, and the new American prevention guidelines

In 2008, the National Heart, Lung and Blood Institute commissioned three expert panels (on cholesterol treatment, blood pressure treatment, and obesity and overweight management) and cross-cutting and supporting work groups (focused on lifestyle and risk assessment) to create updated clinical practice guidelines for cardiovascular disease prevention. The American Heart Association and American College of Cardiology completed and published the guidelines on Nov 12, 2013.[1–4] For the first time, these guideline panels and work groups took an approach that was based almost solely on systematic reviews of the medical literature and synthesis of high-quality evidence.

In their Comment,[5] Paul Ridker and Nancy Cook support many of the recommendations for cardiovascular risk reduction that were made as a result of the prolonged and careful deliberations of these panels. However, they take issue with the risk assessment algorithm provided by the guidelines. For its risk calculator, the work group pooled recent data (mostly derived from the 1990s) from several long-standing, community-based US cohort studies to develop new sex-specific and race-specific equations to predict 10-year risk for atherosclerotic cardiovascular disease (ASCVD).[2] These pooled cohort equations represent a major step forward for risk estimation, because, for the first time in a major guideline, they focus on estimation of risk for both heart attacks and strokes and provide estimates applicable to African American people. As a result, they are much better at representing overall, or global, cardiovascular disease risk, especially in women and African Americans, in whom risk for stroke increases earlier in life than does risk for heart attacks.

The risk assessment work group considered other potential approaches to assess risk for ASCVD, including application of the complex inclusion and exclusion criteria from published clinical trials, but this approach (as suggested by Ridker and Cook) was deemed too difficult to apply routinely or appropriately in clinical practice, and can be prone to error. Most importantly, the approach does not consider the compelling data from tens of thousands of patients treated with statins in rigorous clinical trials showing that the absolute benefit of a statin is proportional to the absolute risk of a patient when based on assessment of all of their risk factor levels (including blood pressure, smoking and diabetes status, age, and sex). Thus, the higher the risk of the patient, the more likely he or she is to benefit substantially from a statin in addition to lifestyle modification as needed. But the recent data also show that benefit extends down even to patients with a roughly 5% risk for ASCVD over the next 10 years.[4]

Importantly, only about 31% of Americans aged 40–75 years without existing cardiovascular disease might be eligible for statin therapy under the new guidelines. This is remarkably similar to what would have occurred under the previous guidelines if the threshold for treatment were lowered modestly from 20% 10-year risk of a heart attack to 10% risk, well short of the threshold of proven benefit in recent trials.[2] Further, many of these patients are likely already on statin therapy, and many would be recommended for treatment by either risk assessment approach.

The risk assessment document[2] (and its supplement) include a detailed explanation of the sophisticated methods used to derive and validate the pooled cohort equations. These equations were subjected to more intensive validation than any other ASCVD risk equations before their publication. Few community-based cohorts have the data and length of follow-up needed to validate these equations. We examined short-term follow-up data from the Multi-Ethnic Study of Atherosclerosis (MESA) and REasons for Geographic And Racial Differences in Stroke (REGARDS) cohorts from the early 2000s. We noted some overestimation of risk by the pooled cohort equations, mainly in high-risk participants, who had fewer events than anticipated. Ironically, this observation might have been due to the very high rates of initiation of statins in high-risk participants after the baseline examinations in MESA (whose participants received their coronary artery calcium score information) and REGARDS.

Ridker and Cook provide some new data from three existing studies suggesting similar over-estimation of risk by the new pooled cohort equations. Individuals in all three cohorts were either screened for participation in, or enrolled in, clinical trials, with the very real potential for healthy volunteer effects. Indeed, event rates in the Women's Health Initiative cohort are remarkably low, and levels of risk factors, such as smoking prevalence, are substantially lower in the Women's Health Study (WHS) and the Physicians' Health Study (PHS) cohorts than in the general US population addressed by the guidelines. In WHS and PHS, some risk factor levels were self-reported in ranges, rather than directly measured, leading to concerns about imprecision. Furthermore, all three cohorts might have been subject to some downstream initiation of statins. We welcome the opportunity for rigorous review of these new data to understand their implications for the risk assessment algorithm.

Because the largest magnitude of any potential overestimation is noted in patients with the highest levels of cardiovascular disease risk, it would not affect the decision to recommend that such a higher-risk patient take a statin. In patients with lower predicted risk, overestimation by the pooled

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cohort equations would be of greater concern. In view of this potential, the cholesterol panel did not recommend statin therapy at the threshold of 5%, at which benefit was suggested by the clinical trial data. Instead, the panel recommended a treatment threshold of 7·5%, creating a buffer against potential overestimation of risk. Importantly, the panel mandated that the patient and clinician engage in a risk discussion before prescription of a statin to understand the sources of the patient's predicted risk, focus attention on potentially modifiable lifestyle factors that could help to mitigate that risk, and provide a balanced perspective on the potential benefits and side-effects or harms of drugs such as statins, which can only be appreciated in context with estimation of absolute risks.[4]

Although we all desire personalised medicine, this goal is still a long way off. No risk assessment algorithm will ever be perfect. These approaches should and will continue to be updated and improved as more data become available. However, quantitative risk assessment using the best available data from broadly representative cohorts that include African Americans, and a focus on an expanded endpoint with stroke as well as heart attack, represents our best hope to identify people at risk who could benefit from a statin.

Sadly, although many people in the USA are asymptomatic for cardiovascular disease, they are hardly healthy; these same individuals who are at risk based on multiple well-defined causal but modifiable risk factors would, in fact, benefit from statin therapy. If left untreated, they will be the individuals who become the statistics that make cardiovascular disease the leading cause of death, disability, lost quality of life, and medical costs in the USA. At present, more than 70 million Americans are regarded as candidates for blood pressure lowering drugs to reduce risk for heart disease and stroke. According to these new guidelines, just more than 30 million people without existing cardiovascular disease might be candidates for statin therapy. These numbers are cause for a call to action to first focus on the prevention of cardiovascular risk factors such as high cholesterol and high blood pressure. Until we get serious about personal lifestyle modification and national policies to promote environmental and behavioural change, we will need blood pressure lowering medications and statins to contain the epidemic of cardiovascular disease.

NJS was Chair of the Cholesterol Guidelines Panel, and DML-J and DG were coChairs of the Risk Assessment Work Group.

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