Response to Comment on the Reports of Over-estimation of ASCVD Risk Using the 2013 AHA/ACC Risk Equation

We appreciate the comments of Muntner et al regarding our concern that the new atherosclerotic cardiovascular risk equation appears to overestimate risk in the 5 external validation cohorts examined to date (Multi-Ethnic Study of Atherosclerosis [MESA], REasons for Geographic and Racial Differences in Stroke [REGARDS], Women’s Health Study [WHS], Physicians’ Health Study [PHS], and Women’s Health Initiative Observational Study [WHI-OS]). We concur that understanding how these validation cohorts differ from those used to derive the new risk equation is important to achieving confidence in the equation.

First, the authors explain that the Atherosclerosis Risk in Communities (ARIC) study contributing to model development used active surveillance to enhance the identification of study outcomes, a technique not used in the REGARDS and MESA studies. Although this is possible explanation for underascertainment in the REGARDS and MESA studies, it is unlikely to have occurred to the same extent in the WHS and PHS cohorts. These are composed of health professionals, who would be more likely to recognize outcomes and report them correctly. In addition, the follow-up response for both of these studies was excellent; morbidity follow-up was 97% and 98% complete in the WHS and PHS, respectively. The follow-up questionnaire response for the WHI-OS was also excellent, with reported recent participation rates of 95% among survivors at study closeout in 2005 and 98% for those in the WHI Extension Study. Although it is conceivable that there may be more underascertainment in the WHI, as the authors noted, this would explain only part of the near doubling of risk in this cohort.

Incident statin use could explain some of the discrepancy and lack of model fit seen in the more contemporary external cohorts, but we believe this effect to be small. Although the results were unchanged when users of lipid-lowering therapy at baseline were excluded in our cohorts, as well as in the external validation cohorts of the committee, there was increasing statin uptake during follow-up. We examined this in detail in the WHS. Only 3% of women were on cholesterol-lowering agents at baseline in the early 1990s, likely nonstatin drugs. This increased to 9% at 4 years, with 7% reporting statin use. By 10 years of follow-up, 22% reported statin use, with use higher as anticipated in higher-risk groups. However, taking into account this increase in statin use over time and assuming both full compliance and a 25% reduction in risk with statin use, predicted rates from the model remain 40% to 100% higher than the observed rates adjusted for such statin use and explain about 8% of the discrepancy on average. Even an optimistic 50% reduction in risk with statins would explain only about 23% of the discrepancy in the WHS estimates.

Increased use of revascularization procedures in contemporary cohorts is a substantive issue because it reflects true clinical practice. In both the WHS and PHS, there were nearly as many of these procedures as there were major atherosclerotic cardiovascular disease events, although there was much overlap. In the WHS, approximately half of those with revascularization procedures had a hard end point either before or after the procedure and would thus be included in the hard end point. However, the increasing use of such procedures is the basis for their inclusion within the principle end point of contemporary randomized trials of statin therapy in primary prevention. Because these trials ultimately must inform evidence-based statin use, a strong argument can be made for including revascularization as an end point for risk calculators as well, an approach we took in our own prediction modeling for the Reynolds risk score. Which outcome is most appropriate to use for risk prediction in contemporary populations is an open issue for discussion.

The fourth point concerns the short-term nature of follow-up in the REGARDS study, which could have led to instability of the estimates. We look forward to the continuing follow-up in the REGARDS cohort and expect that it will provide valuable information, particularly with respect to cardiovascular disease rates among African Americans.

Other explanations for the discrepancies are also plausible. Although the MESA, REGARDS, and WHI-OS studies were designed to be representative US population cohorts, the WHS and PHS were cohorts of health professionals and were part of randomized trials. Although these cohorts were healthier than a general population sample, their low cardiovascular disease risk should be reflected in their risk factors, and the risk calculator should take into account their favorable levels of smoking, diabetes, lipids, and blood pressure. Conversely, baseline measures in the Framingham cohort were taken >30 years ago, when the cohort included a large proportion of current smokers (33% among whites). Although current smoking is included in the model, lingering effects attributable to past or passive smoking may be changing over time as smoking rates decline. In addition, treatment of blood pressure, both at baseline and over time, likely has improved over the past decades. It is not clear how much influence this should have on a risk calculator for contemporary prescription of statins.

It is also important to pay attention to methodologic issues. For example, it is not clear from the description in the report whether any differences among the cohorts were accommodated. Given the small sample sizes, young age, and low event rates in the Coronary Artery Risk Development in Young Adults (CARDIA) study, it is unclear how much that study contributed to the models. The older age and higher event rates in the Cardiovascular Risk Study (CHS) likely contributed many outcome events. Whether the Kaplan-Meier event rates shown and the predicted risk account for deaths attributable to competing causes is unclear. One criticism of the WHS and PHS cohorts has been the use of self-reported blood pressures, although lipids were directly measured. However, in physicians and other health professionals, self-reported blood pressures have been found to be highly accurate when compared with actual measures, which also suffer from measurement variability.

As we described previously, an alternative approach to statin prescription that relies on trial data rather than epidemiologic modeling may avoid some of the limitations inherent in risk prediction modeling. Results of randomized trials in heart failure and renal failure indicate that event reduction cannot be assumed for statin therapy on the basis of high absolute risk alone and that clinical context is important for understanding when statin therapy is effective and when it is not. Thus, it remains controversial whether prescribing statins solely on the basis of modeled risk estimates is, in the end, the most efficient method for drug allocation.

Given that the new risk calculator has overestimated risk in the 5 contemporary external validation cohorts so far evaluated, we look forward to seeing additional data from other cohorts and working toward clinical resolution. In the meantime, we reiterate the opinion voiced in our commentary in *The Lancet* that the new guidelines take several major steps forward that will increase use and intensity of statin therapy among appropriate patient groups. The new guidelines also reinforce critical advice regarding the continued importance of smoking cessation, blood pressure control, exercise, and dietary discretion for our patients. Issues with risk calculations should not distract physicians from implementing these broad and important messages.
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References
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