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

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To the Editor:

We read with interest the comment by Ridker and Cook in The Lancet on the new atherosclerotic cardiovascular disease (ASCVD) risk equation released by the American College of Cardiology (ACC) and American Heart Association (AHA). They showed that the new risk equation overestimates ASCVD risk when applied in several cohort studies. One of these studies was the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, which was used in the ACC/AHA guideline to validate the ASCVD risk equation. As REGARDS investigators, we are writing to provide clarification on design components of REGARDS and other contemporary cardiovascular epidemiology studies cited by Ridker and Cook that could contribute to lower-than-expected event numbers. We offer four possible explanations for the apparent over-estimation of ASCVD risk by the new equation. In our opinion, these explanations suggest the ASCVD risk equation may be more valid than has been suggested by Ridker and Cook.

First, the studies used to develop the ASCVD risk equation included “active surveillance” to supplement self-report for identifying possible events. For example, in the Atherosclerosis Risk in Communities Study (ARIC; one of the studies used in developing the ASCVD risk equation), investigators identified possible ASCVD events using two approaches: (1) study staff telephoned participants or their proxies annually to identify hospitalizations and deaths and (2) they searched lists of ICD codes from area hospitals and state death files. For all death and hospital records that may have involved an ASCVD event, the ARIC study staff abstracted diagnostic information and obtained
Minnesota coding for ECGs. Also, coronary events that occurred out of the hospital setting were documented by study staff who contacted physicians, coroners, and next of kin for information. However, the validation cohorts (REGARDS and the Multiethnic Study of Atherosclerosis [MESA]) and, to our knowledge, the studies evaluated by Ridker and Cook, did not include similar surveillance procedures, which are costly and far less feasible since the implementation of the Health Insurance Portability and Accountability Act of 1996. Thus, these validation cohorts may have missed some CVD events. We previously reported on the inability to retrieve some medical records for suspected stroke events in the REGARDS study, and provided analytical solutions to address this issue. Additionally, in the Women’s Health Initiative Clinical Trial, linkage with Medicare claims found that ~28% of myocardial infarctions were not identified through their event reporting protocol (M Hlatky, personal communication). This underascertainment of events may have a large impact on the absolute CVD incidence rates in the studies included in Ridker and Cook’s editorial. It is unclear how much of the overestimation of CVD incidence in the validation studies is explained by the lack of surveillance components in modern epidemiology studies. However, data from the REGARDS study and Women’s Health Initiative suggests this may be substantial.

Second, the proportion of US adults taking statins has tripled over the past 12 years, as identified by serial National Health and Nutrition Examination Surveys (NHANES). This rapid increase, along with the fact that study participants in the ASCVD risk equation validation studies were given their baseline examination results, which might lead to a statin prescription, could contribute to over-estimation of CVD risk.
in comparison to the observed rates. The REGARDS study is currently conducting a follow-up visit where statin initiation following baseline will be identified. Given the estimated 20% to 30% relative risk reduction for CVD associated with statins in primary prevention\(^7\), initiation of statins after enrollment in REGARDS and MESA probably contributed to the over-estimation of CVD risk observed in the validation cohorts. This may be especially true for the high risk group (ASCVD risk $>10\%$), where the risk equation showed the largest overestimation\(^1\); high risk participants are the population most likely to initiate statins following their baseline study visit, and this group would have the largest absolute risk reduction.

Third, the increased use of revascularization procedures, especially percutaneous coronary interventions (PCI) in the US since the time of the studies used to develop the ASCVD risk equation might also lead to further underestimation of CVD event rates in the contemporary cohorts used for validation\(^8\). The ASCVD risk equation was developed to predict so-called “hard” ASCVD events (i.e., myocardial infarctions, stroke or death from coronary disease or stroke). Revascularization procedures were not included as outcomes\(^2\). For patients with acute coronary syndromes, revascularization procedures have been shown to reduce the incidence of myocardial infarction\(^9\). When compared to optimal medical therapy, revascularization procedures in the setting of stable coronary disease may not delay the occurrence of a myocardial infarction\(^{10, 11}\). However, given the low rate of optimal medical therapy use in the general population\(^{12}\), revascularization procedures may be preventing the onset of some overt events in the contemporary observational cohort studies. Based on these data, it is our opinion that the increased use
of PCI might contribute to the overestimation of event rates in the validation studies. Further, clinical practice guidelines during the time of the validation cohorts recommended that known coronary disease be treated as a high risk condition\textsuperscript{13}, increasing the likelihood that revascularized patients who did not have a hard outcome were initiated on statins, further contributing to lower than expected event rates preferentially among those at highest risk.

Fourth, validation of the ASCVD risk equation in the MESA and REGARDS studies relied on a short follow-up period during which there were a limited number of events. The number of events is especially modest considering that event rate estimates were generated for 16 groups defined by race, sex, and ASCVD risk categories. The most recent data lock for the REGARDS study includes additional follow-up for ASCVD events. Re-analysis of the REGARDS data using the additional events needs to be completed to provide more stable estimates that also reflect longer-term outcome event rates.

In our opinion, these four considerations lead us to the conclusion that it is premature to draw firm conclusions about potential over-estimation of risk using the new ASCVD risk equation. We look forward to using the contemporary data available from the REGARDS study to inform the ongoing discussion surrounding the new ASCVD risk equation.
Disclosures

Dr. Muntner has served on advisory boards and received research grants from Amgen Inc and is an American Heart Association volunteer. Dr. Safford has received research funding from Amgen, Inc. and diaDexus, has served as a consultant for diaDexus, and is an American Heart Association volunteer and a Fellow of the American Heart Association. Dr. Cushman has received research funding from diaDexus and is an American Heart Association volunteer and a Fellow of the American Heart Association. Dr. Howard has no disclosures.
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