Regarding REGARDS: Does Inflammation Explain Racial and Regional Differences in Cardiovascular Disease Risk?

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Although black men and women residing in the US experience the highest rates of mortality from both stroke and coronary heart disease (CHD)3 (1), underlying reasons for these statistics remain uncertain. Although differential traditional risk factors, access to care, and sociodemographic and psychosocial variability between race/ethnic groups might undoubtedly account for some of the observed differences, other factors might be at play. For example, whereas both ischemic stroke and CHD often share atherosclerosis as a core pathogenic element, evidence suggests that in general blacks tend to have less atherosclerotic burden measured by coronary calcium score or angiography than whites (2). Additionally, autopsy results from blacks and whites who succumbed to sudden cardiac death indicate that blacks have a higher preponderance of stable plaque than whites (3). Thus, from a pathological perspective, race/ethnic differences in cardiovascular risk require further elucidation.

The REGARDS (Reasons for Geographic and Racial Differences in Stroke) study was instituted to examine causes for the excess stroke mortality among US blacks and people living in the stroke belt (4). Previous publications from the study examined individual traditional risk factors for stroke and CHD. Differences between blacks and whites and by region were demonstrated—including differences in the prevalence of blood pressure and antihypertensive use was higher among both blacks and whites residing in the stroke belt (4), there was a trend toward better treatment and control of hypertension in this region (5). Similarly, the prevalence of diabetes, particularly among black women, was also higher within each racial group in the stroke “buckle” (parts of North and South Carolina and Georgia) (4, 6). Despite these findings, neither traditional risk factors when combined in the Framingham Stroke Risk Score nor measured socioeconomic variables accounted for regional differences. One caveat of the aforementioned studies is the lack of data on actual stroke events. Nonetheless, these findings raise the hypothesis that other nontraditional factors or unmeasured confounders might contribute to the regional stroke variability.

Building on the above, the article by Cushman and colleagues in this issue of Clinical Chemistry examines the role of inflammation, as measured by highsensitivity assays for C-reactive protein (hsCRP), in stroke risk by race and region (7). More globally, whether hsCRP explains the increase in cardiovascular risk in blacks is unknown. Data from both the Women’s Health Study (8) and the Dallas Heart Study (9) indicated that hsCRP concentrations were highest among black women, and that measures of adiposity contributed significantly to hsCRP concentrations in all race/ethnic groups. Black–white differences were attenuated but not eliminated after adjustment for traditional risk factors. The residual difference could be related to multiple factors or stressors that result in upregulation of hsCRP concentrations.

Data from REGARDS similarly showed that blacks were more likely to have increased hsCRP than whites. The crude 80% higher odds of increased hsCRP among blacks was reduced to 30% after adjustment for other factors, but remained statistically significant. Those residing in the stroke belt had 10% higher odds of having an increased hsCRP. Because hsCRP has been shown in multiple studies to be a predictor of cardiovascular risk, including from both stroke and CHD, these dif-
ferences may contribute to the overall increase in cardiovascular disease (CVD) risk. To date, however, no prospective CVD risk prediction study using hsCRP has been conducted in an adequately powered sample of black individuals.

The authors explored these differences by estimating the risk of later disease using published risk prediction scores. They computed the Framingham Coronary Risk Score (10), the Framingham Vascular Risk Score (11), and the Reynolds Risk Score (12), which incorporates hsCRP as well as other traditional risk factors. Their hypothesis in part was that a combination of the influence of several components of vascular risk including hsCRP could reflect and possibly explain the increased stroke and CHD risk seen among blacks and people living in the stroke belt.

In their analyses, Cushman et al. first showed that values of all 3 scores were somewhat associated with hsCRP, although the association was stronger for the Reynolds Risk Score, indicating that some of the traditional risk factors may be slightly correlated with hsCRP. The authors then estimated the extent of risk reclassification that could occur using hsCRP. In the Women’s Health Study, the Reynolds Risk Score incorporating both hsCRP and family history reclassified 6% of all women in validation data (12). Moreover, the score reclassified approximately 30% of women (12) and 20% of men (13) among those at intermediate risk.

In the current article, however, Cushman et al. were unable to directly compare models fitted with and without hsCRP as in the evaluation of the Reynolds Risk Score. Instead they assumed that all individuals with increased hsCRP (≥3 mg/L) would be reclassified into a higher risk group. This assumption is too simplistic for 2 reasons: first, the effect of hsCRP alone may not be sufficient for an individual to cross risk boundaries, and second, hsCRP may be correlated with other risk factors already in the model which could influence risk in unknown ways. Whereas a high hsCRP may indeed lead to a higher estimated risk stratum, the percentages moving up or down risk categories are likely to be much smaller than those shown in the current article.

In addition, the authors directly compared the estimated risk from different published models. Perhaps contrary to expectations, the median risk was lower for the Reynolds Risk Score for total cardiovascular disease than for the Framingham score for coronary heart disease alone. The median estimated risk for the Framingham Vascular Risk Score was about twice as high as the other 2. Using either of the Framingham scores, the Reynolds score reclassified the vast majority of individuals downward, despite the high prevalence of increased hsCRP.

Why is this? The answer is that the scores are estimating risk for very different outcomes. The Framingham Coronary score evaluated in this report includes several “soft” CHD endpoints, in contrast to the Adult Treatment Panel III (ATP III) score (14), which includes the “hard” outcomes of myocardial infarction and coronary death. Besides these hard outcomes, the coronary score used here includes angina pectoris, unrecognized myocardial infarction, and coronary insufficiency, which could greatly increase the estimated risk. The difference between the 2 Framingham scores is larger in women than in men. Using the average values in Table 1 of the Cushman study (7), the estimated risk for men would be similar with the 2 models, estimated as 13% with the coronary score and 12% with the ATP III score. For women, the difference is larger; estimated risk would be 9% with the coronary score, but only 2% with the ATP III score.

Even a direct comparison of the Framingham Vascular Score with the Reynolds Risk Score is not appropriate. The Reynolds score estimates the risk of MI, stroke, coronary revascularization, and cardiovascular mortality, whereas the Framingham Vascular Score includes these outcomes as well as angina, coronary insufficiency, transient ischemic attack, peripheral artery disease, and heart failure. Given the same traditional risk factors as above, the estimated Framingham vascular risk would be 18% in men and 8% in women. Using the average hsCRP concentrations in REGARDS, the estimated risk with the Reynolds score would be 11% in a man without family history (18% with history) and 3% in a woman without history (5% with history). Clearly the scores are not comparing apples to apples, and the differing endpoints need to be taken into account.

So, does hsCRP explain the differences in stroke risk by race and region? Curiously, the authors did not compare estimated risk levels using the Reynolds Risk Score across these groups. Although the higher proportion with increased hsCRP among blacks suggests that some of the increase in risk may be explained by this marker of inflammation, it is impossible to tell in the current analysis by Cushman et al. In addition, both the Framingham scores and the Reynolds scores were developed and validated in mostly white populations. It thus remains uncertain how accurately either model would estimate risk in nonwhite populations, a factor that might be most evident for black women, who experience their first myocardial infarction almost 5 years earlier than white women (15).

Only follow-up for cardiovascular endpoints can ultimately provide the answer. Although a strong limitation of the current article is the lack of such outcome data, the study intends to follow the participants and collect this important information. Only then will the
true answer become clear. Despite these limitations, the authors should nonetheless be commended for their efforts to understand how commonly accepted risk algorithms might apply to populations besides white individuals.

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References

8. Albert MA, Glynn RJ, Buring JE, Ridker PM. C-reactive protein levels among women of various ethnic groups living in the United States (from the Women’s Health Study). Am J Cardiol 2004;93:1238–42.