EDITORIAL COMMENT

Homocysteine and Cardiovascular Risk

An Old Foe Creeps Back*

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Several scoring systems, based on traditional risk factors, are available for the 10-year quantification of cardiovascular (CV) risk for either coronary heart disease (CHD) or cardiovascular disease (CVD) events. Assessing CV risk is useful to identify patients requiring aggressive management (i.e., high risk) or monitoring (i.e., low risk) or those at intermediate risk. The last group presents treatment challenges and requires a case-by-case approach. Importantly, available scoring systems should only be used in primary prevention (i.e., before the occurrence of a CV event). Patients with previous CV events are considered high risk and should be managed accordingly.

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It is well established that a substantial proportion of CVD events is not accounted for by traditional risk factors (1). Over the last 30 years, a better understanding of atherosclerosis has led to the identification of novel, nontraditional risk factors. For large-scale use, particularly in the current economic climate, such nontraditional risk factors should be: 1) easily and cheaply measurable; 2) related to CV risk in a predictable fashion; and 3) potentially modifiable by means of pharmacological and/or nonpharmacological interventions. Therefore, by definition, nontraditional CV risk factors must predict CVD events. However, their use in clinical practice adds little if they do not substantially increase the capacity to predict CVD over and above traditional risk factors.

Excessive plasma concentrations of the highly reactive sulfur-containing amino acid homocysteine (Hcy) have been long known to adversely affect vascular homeostasis (2). Epidemiological studies have demonstrated a positive and independent association between Hcy concentrations and CVD events (2). The next logical step is determining the clinical utility of measuring Hcy concentrations by assessing both its predictive value, and most importantly, its potential to assist in clinical decision making by reallocating patients to either higher (i.e., aggressive management) or lower (i.e., monitoring) risk categories.

In this issue of the Journal, Veeranna et al. (3) address this topic by running post hoc analyses on the MESA (Multi-Ethnic Study of Atherosclerosis) and NHANES III (National Health and Nutrition Examination Survey III) trials. The predictive power of Hcy was assessed by calculating the area under the receiver operating characteristics curve (AU-ROC) using the Framingham Risk Score (FRS) with and without Hcy concentration. Improvement in risk classification, equally important to risk prediction in quantifying the usefulness of new markers, was measured via 2 relatively new statistics, the net reclassification improvement index (NRI) and the integrated discrimination improvement (IDI) (4). The NRI examines the percentage of patients who were better classified in terms of higher or lower risk based upon their subsequent event status, following the addition of the new variable to the risk prediction algorithm. The IDI, another category-free index very similar in nature to the AU-ROC or C-statistic, assesses the change in the difference of the mean predicted probabilities of the outcome between those with and without the disease; as such, the IDI is not influenced by varying the selection of risk score cut points.

The increases in AU-ROC observed by Veeranna et al. (3) with the addition of Hcy level were of the order of 0.025, indicating an additional 2.5% increase in the probability that someone who had an event had a higher predicted risk than someone who did not. This small increase is typical of models that already contain at least a handful of strong predictors. It is often hard to be convinced that such small changes will translate into meaningful differences in patient management, even if from a public health perspective, changes of this magnitude might be meaningful. Despite the small gains in predictive yield, much greater improvements were obtained in reclassification, with approximately 20% of patients at intermediate risk being better classified, with an overall downward reclassification of risk among the nonevents (3). Mindful of the potential for artificial enhancement of the NRI, which will vary according to selection of the chosen FRS tertile cut points, the authors reanalyzed the NRI using the recently updated “category-free” NRI approach and confirmed their findings (5).

This study provides a sound rationale for adding Hcy in CVD risk assessment. An additional strength was the adjustment for C-reactive protein and markers of renal function, none of which affected either the predictive yield of Hcy for CHD events or risk reclassification.
Although informative, the data from Veeranna et al. (3) need to be interpreted with caution for a number of reasons. First, the FRS is not universally accepted because it assesses CHD risk, rather than CVD risk, although modified versions accounting for CVD events have been introduced (6). Further studies are required to ascertain the role of Hcy concentration in risk reclassification in cerebrovascular disease, peripheral arterial disease, and heart failure. Second, the applicability of the FRS in populations outside the United States is far from established. Whether the results could be replicated using different scoring systems warrants further investigation. Third, the use of the FRS in the NHANES III cohort might be inappropriate because several participants had a history of myocardial infarction or cerebrovascular disease (7,8). As previously discussed, CV risk scores should only be used in patients without previous CV events (i.e., in primary prevention). Fourth, the NRI statistic on its own does not indicate where the improvements in classification occur (i.e., which tertile) and also to whom (those who had the events or those who did not). The modified risk engine was more successful in identifying those who had events than those who did not with 19.4% and 30.3% of patients who had events in MESA and NHANES III, respectively, being correctly reclassified higher compared with 3.0% and 5.7% of patients who did not have events in the 2 respective cohorts being reclassified lower (3). Incorrect reclassification was lower than correct reclassification among patients with events (4.0% and 11.8% were reclassified lower in MESA and NHANES III, respectively) and similar to correct reclassification among patients without events (5.4% and 5.7% were reclassified higher in MESA and NHANES III, respectively). Overall, the NRI was useful in better identifying patients who had a subsequent event, which is the primary objective of the risk engine, but did not better identify those without a subsequent event. In other studies, however, an improved NRI may arise from the opposite scenario; therefore, care needs to be taken when NRI results are evaluated because similar values may arise for different reasons.

Where do we go from here? Notwithstanding the aforementioned issues, a possible step forward is using the results of this study to determine the cost/benefit ratio of including Hcy measurement in population screening programs. Comparing the results with other nontraditional CVD risk markers (e.g., C-reactive protein and coronary artery calcium score) would be useful in the context of public health interventions. Moreover, it is known that Hcy is present in various forms, with different effects on vascular homeostasis (9). Analyzing specific Hcy forms might result in enhanced predictive yield and risk reclassification and alter cost/benefit ratios.

Finally, an important question remains: Because no large randomized controlled trial has demonstrated any beneficial effect of Hcy-lowering therapies on CV outcomes, should we consider Hcy as a mere bystander? Veeranna et al. (3) rightly argue that virtually all such trials have been conducted in patients with advanced atherosclerosis (i.e., either pre-existing CVD or very high risk). If Hcy is to be used as a screening tool in primary prevention, it is imperative that further trials are conducted in low- and intermediate-risk patients without previous CVD. Only then can the real value of measuring Hcy as a nontraditional CVD risk factor or risk marker be quantified.

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