To the Editor:

Malinow et al, in their recent review on homocysteine and cardiovascular diseases, correctly state that based on the available evidence, it is premature to conclude that total homocysteine (tHcy) plasma levels are predictive of the development of cardiovascular events. Their conclusion is mostly based on the analysis of the results of prospective cohort studies of tHcy in cardiovascular diseases, which were conflicting. In my opinion, among the possible explanations for the different results of prospective cohort studies, the effects of different cardiovascular risk profiles among the populations studied should be considered. Therefore, when analyzing the results of prospective cohort studies of the risk of future cardiovascular events associated with hyperhomocysteinemia, it is important to differentiate between studies of individuals who were healthy at the time of their enrollment and those of patients with overt cardiovascular disease or other conditions at risk. Of 11 studies of individuals who were healthy at the time of their enrollment, 5 demonstrated that high homocysteine levels are associated with an increased risk of future cardiovascular diseases, whereas 6 failed to show such an association (reviewed in Reference 2). A twelfth prospective study, which was published recently, revealed that, in elderly men followed up for 10 years, tHcy was a predictor for fatal cerebrovascular disease, but less so for coronary heart disease. In contrast to the conflicting results of studies of healthy individuals, 4 studies of patients with overt cardiovascular disease, or other conditions at risk, such as systemic lupus erythematosus and end-stage renal disease, consistently showed that tHcy levels predicted the risk of future cardiovascular events (reviewed in Reference 2). These results are consistent with the hypothesis that homocysteine is by itself a mild risk factor for cardiovascular disease but could substantially contribute to the development of vascular occlusions in patients at high risk. In line with this hypothesis is the observation that one of the very rare case-control studies that failed to show an association between hyperhomocysteinemia and the risk of myocardial infarction was carried out in patients with a low cardiovascular risk profile.

Therefore, screening for plasma tHcy levels is probably not justified in healthy individuals at low cardiovascular risk but may be advisable in individuals at high risk. Ongoing clinical trials will soon tell us whether these patients will benefit from treatment with homocysteine-lowering vitamins.

Marco Cattaneo
Angelo Bianchi Bonomi Hemophilia and Thrombosis Center
Department of Internal Medicine
IRCCS Ospedale Maggiore, University of Milano
Milano, Italy


Response

We appreciate the comments of Dr Cattaneo. The twelfth recently published prospective study that he quotes was not available to us at the time our article was written. However, the inclusion of that observation would not change our conclusion regarding the lack of consistent results from prospective studies of homocyst(e)ine and cardiovascular disease risk.

In agreement with Dr Cattaneo, our article did include criteria for considering homocyst(e)ine measurements in certain high-risk patients. We indicated that there is insufficient evidence from prospective studies to support widespread screening of patients at apparently low risk of coronary artery disease. Ultimately, clear guidelines for screening homocyst(e)ine determinations cannot be formulated until the results from clinical trials of the effects of homocyst(e)ine lowering on recurrent and de novo cardiovascular disease outcomes are available.

M. René Malinow, MD
Oregon Regional Primate Research Center
Beaverton, Ore

Andrew G. Bostom, MD
Division of General and Internal Medicine
Memorial Hospital of Rhode Island
Pawtucket, RI

Ronald M. Krauss, MD
Lawrence Berkeley National Laboratory
University of California
Berkeley, Calif
Homocysteine and Cardiovascular Diseases
Marco Cattaneo

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