Is Homocysteine a Risk Factor for Atherothrombotic Cardiovascular Disease?

In a recent state-of-the-art study, Kaul et al. (1) have not validated the hypothesis of homocysteine as a risk factor for atherothrombotic cardiovascular disease. These conclusions will have major implications for the developing countries that derive cutting-edge knowledge of cardiovascular disease from the West (2).

There is consistency in the mean homocysteine level in patients with coronary artery disease (CAD) from Pakistan and India of about 19 μmol/l (3–8). This finding is significant because the South Asian population has the highest known rate of CAD, which is widespread, early onset, and aggressive (9). In view of the mandated fortification of food products in the U.S., it was predicted beforehand that the statistical power of the ongoing trials would be marked by power shortage (15).

Ironically, the trend-setting study “Folate Therapy and In-Stent Restenosis After Coronary Stenting” (16) in its conclusion never mentioned the trend toward the beneficial effect of folate replacement in patients with homocysteine levels >15 μmol/l, and the study became a landmark trial showing increase risk of in-stent restenosis with folate therapy, which was documented in patients with homocysteine levels <15 μmol/l.

The scenario is further biased by the fact that after folic acid fortification in the United States, a population-wide reduction in blood homocysteine concentration has been seen; according to one estimate, the proportion of patients with homocysteine >15 μmol/l decreased from 41% to 28%. This mean decrease in homocysteine levels in this population has nicely translated in terms of trend toward mortality benefit in cardiovascular disease and definite improvement in stroke-related mortality (17,18). These facts are well appreciated by Kaul et al. in defining the therapeutic range of high-risk individuals in the recommendations for screening and treatment of elevated homocysteine levels.

How do developing countries, which form a major chunk of global burden (2) of cardiovascular disease, reconcile with the invalidation of homocysteine hypothesis for atherothrombosis? In the long run, its repercussions could be in the form of the 10/90 gap, which refers to the global situation where only 10% of billions of dollars is devoted to health research, which accounts for 90% of total health burden (19).

Finally, this state-of-the-art study is food for thought in context to the philosophy to achieve maximum diversity nicely highlighted by Anthony DeMaria in the Journal’s Editor’s Page, “Diversity in JACC” (20).

REFERENCES

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The data from the 3 largest completed trials of homocysteine lowering with folic acid and vitamin B12, with or without vitamin B6 (VISP [Vitamin Intervention for Stroke Prevention] [1], NORVIT [Norwegian Vitamin Trial] [2], and HOPE-2 [Heart Outcomes Prevention Evaluation] [3]) consistently demonstrate no treatment benefit in patients with established vascular disease. These trials primarily evaluated white, middle-aged patients exposed to folate-fortified food (70% in HOPE-2, 100% in VISP) with only mild increases in homocysteine levels (<15 μmol/l). We agree that homocysteine-lowering therapy might potentially still prove to be beneficial in populations other than those studied—for example, in Southeast Asian patients where homocysteine levels typically exceed 15 μmol/l related to genetic or dietary factors, as suggested by Dr. Akhtar. However, subgroup analyses of the NORVIT and HOPE-2 trials provide useful insights. In 40% of patients in the NORVIT trial with a baseline homocysteine level above 13 μmol/l (mean homocysteine level was 17.4 μmol/l in this subgroup), homocysteine-lowering therapy provided no benefit. Similarly, no treatment benefit was observed among patients in the upper fifth of the baseline homocysteine distribution (≥19.7 μmol/l) in HOPE-2. It is quite possible that this lack of benefit may be related to inadequate statistical power in these subgroups. Thus, whether homocysteine-lowering therapy is going to be beneficial cannot be answered definitively until prospective, randomized trials are conducted in these populations. Ongoing large trials that are currently exploring these issues and the planned meta-analyses of all trials (12 trials involving about 52,000 participants with adequate statistical power, 7 in populations without fortification, and 5 in populations with fortification) (4) might help answer remaining relevant clinical questions.

With regards to folate therapy and in-stent restenosis, we do mention in our article (5) (p. 916) that slight, but not significant, benefits were observed in patients with elevated homocysteine levels (27.2% vs. 31.7%, p = NS).

A causal link between recent trends toward a lower rate of death from stroke in the U.S. and Canada and the fortification of food with folic acid remains speculative, as many other factors may have contributed to the decline (6).

Finally, we agree with Dr. Akhtar that a major obstacle to developing tools that address health problems of people in developing countries is the so-called 10/90 problem, whereby 90% of health research expenditure is targeted at problems affecting only 10% of the world’s population. Investment in health, both at the individual country level and at a global level, should therefore be encouraged to provide the necessary resources to develop these tools and enhance public health.

*Sanjay Kaul, MD
Andrew A. Zadeh, MD
Prediman K. Shah, MD
*Cedars–Sinai Medical Center
Cardiology
South Professional Tower
Room 5536
8700 Beverly Boulevard
Los Angeles, California 90048-1804
E-mail: kaul@cshs.org

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