The paradigm that homocysteine is associated with atherosclerotic disease has been discussed since the 1960s. Since then, large observational studies and meta-analyses showed a strong relationship between homocysteine and cardiovascular risk. However, several recent trials using homocysteine-lowering therapies for secondary prevention failed to show beneficial effects in patients with prior stroke or known coronary artery disease.1−3 These trials showed no advantage of either folic acid and/or vitamin B complex therapy on “hard” end points such as mortality or cardiovascular events. Thus, the “homocysteine hypothesis” for atherothrombotic disease became controversial. Kaul et al4 stated in a recent review that it remains unclear whether a causal relationship exists between homocysteine and cardiovascular risk, or if homocysteine is related to other confounding risk factors or is a marker of existing disease burden.

This discussion is now continued and refuelled with a new study published in this issue of Stroke. Hodis and coworkers present a work that assesses homocysteine-lowering therapy as primary prevention in patients without preexisting cardiovascular disease. The goal was to show a reducing effect of a high-dose combination of B-vitamins on progression of carotid intima media thickness (IMT), a marker of early subclinical atherosclerosis, and coronary as well as aortic calcification. Although the originally planned observation time was extended to gain more power for the statistical analysis, the therapy lowered homocysteine levels but did not reduce the progression of any of these end points. However, a subgroup analysis of subjects with a baseline homocysteine above the median (≥9.1 μmol/L) did reveal a treatment effect. In this subgroup the progression of IMT and thus early atherosclerosis was significantly reduced. Interestingly, these subjects presented with lower initial vitamin B levels.

This study naturally raises several questions: (1) What patients potentially benefit from homocysteine-lowering therapies?; (2) Is there an optimal dose?; (3) What end points or tools for risk stratification should be used?

The “holy grail” of primary prevention remains to be the identification of asymptomatic patients with high vascular risk.6 The assessment of IMT is a well established surrogate marker for cardiovascular risk. Progression of IMT as a marker of early atherosclerosis and its progression focuses on structural changes of the vascular wall over time. This study was, unfortunately, underpowered to detect relevant changes across the given timeframe and the chosen intervention, and only subgroup analysis was able to show a treatment effect.

To earlier detect changes of the vascular wall, a combination of available techniques combining morphological and functional aspects may yield more insight into pathophysiological processes: although there is only a limited correlation with IMT, flow mediated vasodilation of the brachial artery is a valuable research tool.7,8 This information can be complemented with physicomechanical parameters: functional, structural and physicomechanical parameters can be quantified using high resolution ultrasound.9 A combination of these parameters and the possible development of a score that could also implement biomarkers as a “multiple-level biomarker strategy”10 may allow to develop a surrogate parameter that could yield a high sensitivity and specificity for the detection of early stage atherosclerotic changes, and to ultimately assess vascular risk. This may be a necessary prerequisite to perform interventional trials for primary prevention with enough power to detect therapeutic effects. A recent work already combined IMT and flow mediated vasodilation assessment in a small secondary prevention sub-
group of the VITATOPS trial. They were able to see only short-term and no long-term efficacy. However, this high risk population with potentially more advanced vascular disease does not reflect the situation of low-risk primary prevention.

Although Hodis and coworkers show some effect on a surrogate parameter of vascular health (IMT), the level of evidence is limited. The final question remains whether high dose vitamin B and folic acid supplementation is a valid approach to reduce cardiovascular outcome. To answer that question, another mega-trial would be needed. It is doubtful whether such a trial would be funded by either public or industry sponsors.

Working in the cardiovascular field we all know at least one colleague pursuing a personal “vascular protection program” of Mediterranean food, red wine, dark chocolate, and physical activity, and who in view of this trial would consider to take additional vitamin B supplementation, not caring about the level of evidence. However, does that mean that we can recommend vitamin B supplementation to lower homocysteine levels to patients? Although it may be a safe therapy, the level of evidence remains low. Thus it will be your choice, until further evidence is gathered.

Disclosures
None.

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The Art of Primary Prevention and Risk Assessment: Homocysteine Revisited
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Stroke. 2009;40:670-671; originally published online December 31, 2008;
doi: 10.1161/STROKEAHA.108.537100
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/40/3/670

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