Homocysteine Lowering in End-Stage Renal Disease
Is There Any Cardiovascular Benefit?

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In 1969, McCully reported an association between homocystinuria, a rare metabolic disorder characterized by high blood levels (>100 μmol/L) of the amino acid homocysteine (Hcy), and severe atherosclerosis among postmortem subjects.1 His report is widely recognized as the basis for the “homocysteine hypothesis,” namely, that elevated blood Hcy is a risk factor for cardiovascular disease (CVD). Since then, a wealth of supporting observational epidemiological evidence has accumulated. In a 2002 meta-analysis of 11 prospective cohort studies of individuals without a history of disease. Nevertheless, the question of whether Hcy is a CVD risk factor persists for several reasons.

First, laboratory investigations point to the role of Hcy in activating pathways attributed to atherogenesis and thrombosis, such as endothelial dysfunction, inflammation, oxidative stress, and endoplasmic reticulum stress.7,8 Animal studies show that dietary methionine-induced Hcy elevations enhance atherogenesis in the presence of high blood lipids.7,9 Second, observational and nonrandomized intervention studies indicate that treatment of patients with homocystinuria with folic acid and B vitamins reduces Hcy and mortality.10,11 Third, carriers of gene variants disruptive of 1-carbon metabolism have higher Hcy levels and CVD risk. Meta-analysis indicates that TT carriers of the C677T variant in the methylene tetrahydrofolate reductase (MTHFR) gene have a 2- to 3-μmol/L higher Hcy level and a 16% to 20% higher risk of coronary heart disease than CC carriers.12,13 Fourth, there are some concerns about the internal validity of the RCTs that attempted to reduce Hcy and CVD risk. Controversial issues include the window of exposure, because Hcy lowering may be unable to halt the progression of established disease in secondary prevention studies; length of follow-up, because the small overall impact of decreased Hcy may translate to low event rates; and impact on specific (eg, stroke) rather than composite CVD disease end points.14

In particular, baseline Hcy level appears to be important. A 1998 meta-analysis of 12 RCTs evaluating the effects of folic acid and B vitamins on Hcy showed that reductions in Hcy are significantly greater when the pretreatment Hcy level is high.15 Interestingly, folate fortification of the North American grain supply (0.1 mg/100 g of flour) began in the same year to combat the incidence of neural tube defects, which had the added effect of lowering the population mean of Hcy from ~12 to 8 μmol/L.16 As a consequence, the ability of folic acid to reduce Hcy among North Americans was reduced from 25% to 16%.16 This point was not considered in the design of some RCTs, and it is unclear whether folic acid fortification contributed to the null findings among the trials.14

Patients with chronic kidney disease are of particular interest for testing the homocysteine hypothesis. Chronic kidney disease represents a spectrum of kidney dysfunction, of which end-stage renal disease (ESRD) is the most serious form. ESRD is characterized by a glomerular filtration rate <15 mL·min⁻¹·1.73 m² and requires regular dialysis and eventually kidney transplantation.17 Patients with ESRD have Hcy levels between 25 and 35 μmol/L, depending on whether or not they come from an area where folic acid fortification is used, and experience a CVD mortality rate 10 to 20 times higher than the general population.18,19 They also have high mortality rates due to a variety of other conditions, including cachexia, cancer, and septicemia.20 In a recent meta-analysis by Heinz et al,19 a 5-μmol/L increase in Hcy was associated with a 9% increased risk of CVD among patients with ESRD.

In this issue of Circulation, Heinz et al sought to further test this relationship in an RCT.21 Heinz and colleagues randomized 650 patients with ESRD attending dialysis clinics to a folic acid and vitamin B12 group and a low-dose placebo group. Participants were followed up for a median of 2 years, during which time 102 deaths occurred in the treatment group.
and 92 in the placebo group. Although there was no significant reduction in total mortality (hazard ratio 1.13, $P=0.51$), which might be expected owing to the multiple causes of death in this group, there was suggestive evidence of a reduction in a composite of CVD events (hazard ratio 0.80, $P=0.13$). In their meta-analysis, Heinz et al. noted among intervention studies an overall 27% decreased risk of a CVD event (relative risk 0.73, $P=0.02$) among 3 studies that did not use supplementation or dietary therapy in the placebo group. These studies all achieved a mean Hcy decrease of at least 13 μmol/L (40%) in the treatment group compared with the control group. A null association was observed among those using supplementation in the placebo group or in those studies that included all-cause mortality in the outcome (relative risk 1.01, $P=0.9$).

What does this mean for the homocysteine hypothesis? Individually, the present study adds little weight to either side of the argument because of its small size, although its results do appear to be in line with the previous meta-analysis. Clearly, more trials are required to supplement the meta-analysis; ideally with large sample sizes to detect the potentially small effect of Hcy lowering on CVD end points.23 In clinical practice, there is little justification to treat patients with ESRD with folic acid and B vitamins. Nevertheless, the American Heart Association currently recommends a diet containing foods with adequate amounts of these components.23 Green leafy vegetables and whole grains are high in folic acid and are both important parts of a prudent dietary pattern that protects against the development of CVD.24

One issue that has not been considered concerns the potential interactions between genetic variants and diet. It has been shown that the MTHFR genotype has a much weaker association with Hcy in fortified populations.25 Interestingly, the MTHFR C677T variant has a stronger association with CVD risk among unfortified East Asian populations than among similar unfortified populations of white Europeans.26,27 Could this represent an interaction between MTHFR and a unique dietary component other than folic acid (eg, methionine or vitamin B12), or possibly a gene-gene interaction unique to ancestral origin? Answers to both of these questions are unknown and require further exploration.

In summary, the present study by Heinz and colleagues makes an important contribution to the understanding of the effects of Hcy lowering in ESRD and adds further depth to a complex issue; however, no definitive conclusion can be drawn about the cardiovascular effects of Hcy lowering among patients with ESRD. Because of the relatively small numbers of CVD end points from this and other trials, larger RCTs, especially among patients with ESRD, are required to resolve this issue. A trial in an undernourished population with high Hcy levels and CVD risk such as in rural China or India would also be helpful to address potential gene-diet interactions. At present, the attainment of adequate dietary folate, which remains an important strategy for cardiovascular health, should come from foods rather than supplements. Prevention and control of major risk factors such as being overweight, smoking, unhealthy diet, physical inactivity, dyslipidemia, hypertension, and diabetes mellitus will certainly remain the dominant strategy for reducing CVD risk.

Disclosures
None.

References


**Key Words:** Editorials, atherosclerosis, nutrition, kidney, prevention
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Circulation. 2010;121:1379-1381; originally published online March 15, 2010;
doi: 10.1161/CIR.0b013e3181daa7c9
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/121/12/1379

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