Lowering Homocysteine With B Vitamins in Patients With Coronary Artery Disease Reply

Marta Ebbing; Per Magne Ueland; Ottar Nygård

JAMA. 2008;300(24):2853-2854 (doi:10.1001/jama.2008.838)

http://jama.ama-assn.org/cgi/content/full/300/24/2853-a

Lowering Homocysteine With B Vitamins in Patients With Coronary Artery Disease

To the Editor: The results of the randomized trial of lowering homocysteine with B vitamins in patients with coronary artery disease (CAD) by Dr Ebbing and colleagues[1] deserve comments. Many studies have shown that hyperhomocysteinemia predicts cardiovascular events,[2] but they have not clarified the shape of this relationship.[3]

Similar to other studies, the Western Norway B Vitamin Intervention Trial (WENBIT) was based on the hypothesis that the relationship between plasma homocysteine and risk of cardiovascular events is linear over the entire range of plasma homocysteine values. However, more than 90% of the patients had normal plasma homocysteine values and only 9.6% had mild-to-intermediate hyperhomocysteinemia,[1] and it does not seem plausible to expect any benefit from correcting a risk factor that is not present. The relationship of other causal cardiovascular risk factors (such as elevated blood pressure[4]) appears to be exponential, the risk being absent or very low below a certain threshold and increasing only beyond that threshold. The same likely applies to plasma homocysteine.

Consistent with this view is a study showing that persons with plasma homocysteine above the median population values were at higher risk of cardiovascular death than those below that value.[5] This implies that it would require a (probably unfeasibly) large study to be adequately powered to show any benefit of plasma homocysteine lowering, and negative studies are likely to be hampered by type 2 error. The shorter than planned follow-up and the power calculations in the WENBIT study are not reassuring against this error. In a previous negative study, when the analysis was confined to patients with hyperhomocysteinemia and adequate vitamin B_{12} supplementation and without renal dysfunction, a significant 21% reduction of cardiovascular events was observed.[2]

Moreover, it seems unusual that all-cause mortality was included in the primary end point, because homocysteine has been mainly indicted as a cardiovascular risk factor. The inclusion of participants who died of accidents, suicides, cancer, and other causes likely further precluded detection of any beneficial cardiovascular effect of plasma homocysteine lowering.

Studies should focus on individuals with hyperhomocysteinemia in which a benefit can reasonably be expected.

Gian Paolo Rossi, MD
gianpaolo.rossi@unipd.it
Teresa Maria Seccia, MD, PhD
Achille C. Pessina, MD, PhD
Department of Clinical and Experimental Medicine
University of Padova
Padova, Italy

Financial Disclosures: None reported.

1. Ebbing M, Bleie Ø, Ueland PM, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. *JAMA*. 2008;300(7):795-804.
2. Herrmann W, Herrmann M, Obeid R. Hyperhomocysteinaemia: a critical review of old and new aspects. *Curr Drug Metab*. 2007;8(1):17-31.
3. Rossi GP, Seccia TM, Pessina AC. Homocysteine, left ventricular dysfunction and coronary artery disease: is there a link? *Clin Chem Lab Med*. 2007;45(12):1645-1651.
4. Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation*. 2005;111(14):1777-1783.
5. Cesari M, Zanchetta M, Burlina A, et al. Hyperhomocysteinemia is inversely related with left ventricular ejection fraction and predicts cardiovascular mortality in high-risk coronary artery disease hypertensives. *Arterioscler Thromb Vasc Biol*. 2005;25(1):115-121.

To the Editor: In the WENBIT study, Dr Ebbing and colleagues[1] reported a significant 30% reduction in baseline homocysteine levels (from 10.8 µmol/L to 7.6 µmol/L) in the active treatment group (folic acid and vitamin B_{12}) after 1 year of treatment. However, both mean baseline and final homocysteine levels were within the normal range (<15 µmol/L), meaning that homocysteine was reduced to a lower value from a higher but still normal value.

It is possible that a beneficial effect might have been identified if the study included solely patients with hyperhomocysteinemia. The Homocysteine Lowering Trialists' Collaboration[2] found that the reduction in homocysteine produced by folic acid supplements was greater at higher pretreatment homocysteine concentrations. Therefore, if the WENBIT study enrolled only patients with hyperhomocysteinemia, greater homocysteine reduction would have been expected, with possibly greater and significant reduction in primary or secondary clinical end points.

The WENBIT study was not designed to test this hypothesis. Only 9.6% of participants in this study had baseline homocysteine levels above the normal range. Moreover, most of these patients with hyperhomocysteinemia had only mild hyperhomocysteinemia (15-30 µmol/L) and only 0.8% of

Letters Section Editor: Robert M. Golub, MD, Senior Editor.

participants had intermediate hyperhomocysteinemia (30-100 µmol/L).

The WENBIT study did not demonstrate a beneficial effect of homocysteine-lowering therapy on cardiovascular risk and, in concordance with VISP, HOPE-2, NORVIT, CHAOS-2, and WAFACS trials,[3] provides strong evidence against the use of B vitamins as a preventive intervention for cardiovascular disease. However, the effect of homocysteine-lowering therapy on cardiovascular risk in patients with hyperhomocysteinemia is still in question and should be evaluated in randomized trials. Perhaps the planned collaborative meta-analysis of pooled data will lead to valuable conclusions about this issue.[4]

George Ntaios, MD
ntaiosgeorge@yahoo.gr
Christos Savopoulos, MD
Apostolos Hatzitolios, MD
First Propedeutic Department of Internal Medicine
AHEPA Hospital
Thessaloniki, Greece

Financial Disclosures: None reported.

1. Ebbing M, Bleie Ø, Ueland PM, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. *JAMA*. 2008;300(7):795-804.
2. Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. *BMJ*. 1998;316(7135):894-898.
3. Lonn E. Homocysteine-lowering B vitamin therapy in cardiovascular prevention: wrong again? *JAMA*. 2008;299(17):2086-2087.
4. Clarke R, Armitage J, Lewington S, Collins R; B-Vitamin Treatment Trialists' Collaboration. Homocysteine-lowering trials for prevention of vascular disease: protocol for a collaborative meta-analysis. *Clin Chem Lab Med*. 2007;45(12):1575-1581.

To the Editor: The WENBIT study by Dr Ebbing and colleagues[1] appears to refute the hypothesis of homocysteine as a cardiovascular risk factor. However, some important aspects were not considered in the article's discussion.

Homocysteine is a long-term risk factor. In the Gothenburg study,[2] women with a high homocysteine level showed a higher mortality only after a follow-up of more than 15 years. Thus, short-term follow-up after cardiovascular events will probably not be able to demonstrate a benefit of B vitamins.

Furthermore, there seems to be no continuous correlation between homocysteine and cardiovascular risk below a threshold of homocysteine level of 12 µmol/L.[2] In prospective studies, only participants in the highest quintile of baseline homocysteine had a significantly increased risk.[3] In the WENBIT study, the mean homocysteine level at baseline was so low (approximately 11 µmol/L) that this would not be expected to act as a risk factor at all. It would require a subgroup analysis of participants with a high baseline homocysteine level to have sufficient statistical power to determine if B vitamins have a benefit.

Unlike hypercholesterolemia, in which lowering low-density lipoprotein may lead to plaque regression, it may be that hyperhomocysteinemia is a one-way road where it is only possible to stop progression. Perhaps trials such as the WENBIT study start too late in the disease process. The question remains whether persons without cardiovascular disease and with a low level of other risk factors but with relevant hyperhomocysteinemia (>15 µmol/L) may benefit from B vitamins. Such a primary prevention study would be long-term (probably requiring at least 15 years of follow-up), would need large numbers to have the necessary statistical power, and thus would be very expensive. This makes it unlikely to ever be undertaken.

Johannes Scholl, MD
scholl@preventionfirst.de
Prevention First–Private Practice for Preventive Medicine
Munich, Germany

Financial Disclosures: None reported.

1. Ebbing M, Bleie Ø, Ueland PM, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. *JAMA*. 2008;300(7):795-804.
2. Zylberstein DE, Bengtsson C, Björkelund C, et al. Serum homocysteine in relation to mortality and morbidity from coronary heart disease: a 24-year follow-up of the population study of women in Gothenburg. *Circulation*. 2004;109(5):601-606.
3. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA*. 2002;288(16):2015-2022.

In Reply: Dr Rossi and colleagues, Dr Ntaios and colleagues, and Dr Scholl make the important point that the lack of proven benefit from homocysteine-lowering treatment by folic acid and vitamin B_{12} in the WENBIT study could be attributed to the fact that most of the 3090 participants had normal plasma levels of total homocysteine at baseline.

At the time the WENBIT study was designed, data from a prospective study of 587 patients from Western Norway with angiographically confirmed CAD demonstrated a strong and graded relationship between plasma total homocysteine levels at baseline and overall mortality after a median follow-up of 4.6 years.[1] Using plasma concentrations of less than 9 µmol/L as reference, mortality ratios adjusted for multiple risk factors were 1.9 for patients with plasma concentrations of 9.0 to 14.9 µmol/L.[1] These and similar results from other observational studies during the 1990s suggested a dose-response relationship across the entire range of homocysteine concentrations. This contention was supported by our observation that baseline level of total homocysteine in plasma was a significant predictor of the primary end point in the WENBIT study.

Dr Rossi and colleagues also suggest that the inclusion of all-cause (rather than cardiovascular) mortality in the composite primary end point could wash out a possible effect on cardiovascular outcomes. We chose all-cause mortality as part of the composite primary end point because of the

relationship between homocysteine levels and overall mortality noted here. Also, by combining all-cause mortality with the selected nonfatal cardiovascular events, we could address event-free survival in an undistorted manner.[2]

The patients in the WENBIT study were optimally treated by conventional medication and procedures, and event rates were lower than anticipated. In addition, follow-up was shorter than planned. Thus, we agree with Dr Rossi and colleagues that the possibility of a type 2 error in the WENBIT study cannot be disregarded. We also agree that it would be useful to test the homocysteine hypothesis of vascular disease in patients with hyperhomocysteinemia and without renal dysfunction. Ideally, the study of the effect of homocysteine-lowering B-vitamin treatment should be extended to larger trials with participants recruited from the general population and followed up over a longer time, to assess whether such treatment could prevent CAD and other cardiovascular diseases. Given the neutral results from most published homocysteine-lowering trials[3] and the total costs of randomized controlled trials, such primary prevention trials will probably never be conducted. It is therefore of major importance that the results from ongoing trials are published and that planned collaborative meta-analyses of pooled data are performed.[4] The combined analyses and long-time follow-up in the 2 CAD populations of the NORVIT[5] and the WENBIT studies may provide additional information about the health effects from treatment with folic acid and other B vitamins.[6]

Marta Ebbing, MD
marta.ebbing@helse-bergen.no
Department of Heart Disease
Per Magne Ueland, MD, PhD
Section for Pharmacology
Institute of Medicine
University of Bergen
Ottar Nygård, MD, PhD
Department of Heart Disease
Haukeland University Hospital
Bergen, Norway

Financial Disclosures: Dr Ueland reported being a member of the steering board of the nonprofit Foundation to Promote Research Into Functional Vitamin B_{12} Deficiency and receiving consulting fees from Nycomed. Dr Nygård reported receiving consulting fees from Nycomed. Dr Ebbing reported no disclosures.

1. Nygård O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med*. 1997;337(4):230-236.
2. Lubsen J, Kirwan BA. Combined endpoints: can we use them? *Stat Med*. 2002; 21(19):2959-2970.
3. Lonn E. Homocysteine-lowering B vitamin therapy in cardiovascular prevention: wrong again? *JAMA*. 2008;299(17):2086-2087.
4. Clarke R, Armitage J, Lewington S, Collins R; B-Vitamin Treatment Trialists' Collaboration. Homocysteine-lowering trials for prevention of vascular disease: protocol for a collaborative meta-analysis. *Clin Chem Lab Med*. 2007;45(12):1575-1581.
5. Bønaa KH, Njølstad I, Ueland PM, et al; NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med*. 2006;354(15):1578-1588.
6. NORVIT and WENBIT: long-term follow-up (NORVIT-WENBIT). ClinicalTrials.gov Web site. http://www.clinicaltrials.gov/ct2/show/NCT00671346?term=nct00671346&rank=1. Accessed September 24, 2008.

Erythropoiesis-Stimulating Agents in the Treatment of Cancer-Associated Anemia

To the Editor: The systematic review and meta-analysis of the effects of erythropoiesis-stimulating agents (ESAs) in the treatment of cancer-associated anemia by Dr Bennett and colleagues[1] was largely based on our previously published Cochrane review,[2,3] supplemented with additional data from the literature. We have a number of concerns about the study methods and data.

First, it is unclear whether the authors followed a protocol that defined eligibility criteria and preplanned subgroup analyses. The eligibility criteria appear to be different from the Cochrane review. Bennett et al incorporated data from ongoing studies[4] and trials with iron supplementation in the active study group, which were excluded from the Cochrane review. If the earlier review was the point of departure for their analysis, only supplemented with studies published after 2005, it does not seem appropriate to use different inclusion and exclusion criteria. All studies published before 2005 should have been re-examined for consistency with the revised criteria.

Second, it appears that the changed eligibility criteria were not consistently applied. Interim results were available for a number of studies that were not included in their analysis.[5,6] They did not include a study with iron supplementation only in the active study group.[7]

Third, for several studies[8-10] the information was not updated based on more recent publications.[11-13] For example, in the analysis by Bennett et al, a study by Savonije et al was included, but they used data based on a conference presentation from 2004[14] that reported 12 deaths out of 211 ESA patients and 6 deaths out of 104 control patients. However, the full publication from July 2005[15] reported 12-month data of 131 deaths in the ESA group and 61 deaths in the control group. For mortality data from the GBR-07 study, Bennett et al cited Food and Drug Administration (FDA) briefing documents for the Oncologic Drug Advisory Committee (ODAC) 2007 (their reference 12), but the numbers of deaths used in the analysis appear to be those from briefing documents for ODAC 2004; more recent data for this study were also available.[16] It is not clear why the most recent data from all studies were not used in their analysis.

Julia Bohlius, MD, MScPH
jbohlius@ispm.unibe.ch
Institute of Social and Preventive Medicine
University of Bern
Bern, Switzerland
Andreas Engert, MD
First Department of Internal Medicine
University Hospital Cologne
Cologne, Germany
Guido Schwarzer, MSc, PhD
Institute of Medical Biometry and Medical Informatics
University of Freiburg
Freiburg, Germany