JACC: ASIA VOL. 4, NO. 8, 2024

EDITORIAL COMMENT

Homocysteine and Myocardial Injury

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In this issue of *JACC: Asia*, Tan et al[1] report on the association of plasma total homocysteine (tHcy) with markers of myocardial injury. They assessed high-sensitivity troponin T, high-sensitivity troponin I, and N-terminal pro-B-type natriuretic peptide. Among 10,871 participants without diagnosed cardiovascular disease (CVD), they found that tHcy was consistently related to myocardial injury. The investigators suggest that the effect of tHcy on myocardial injury contributes to the increased cardiovascular mortality from hyperhomocysteinemia.

Their paper adds to the strong evidence that hyperhomocysteinemia aggravates atherosclerosis, and increases the risk of stroke and other forms of CVD. An important part of the mechanism for increased risk of stroke and CVD is hypercoagulability due to hyperhomocysteinemia, with increased risk of venous thrombosis in addition to increased risk of arterial events.

Although it is widely accepted that hyperhomocysteinemia increases CVD risk,[2,3] it is less well understood that vitamin therapy to lower tHcy reduces the risk of stroke, if not of other CVD events. During an educational program of the Canadian Stroke Consortium in 2023, the speaker polled the audience before a talk about homocysteine and stroke; the results were astounding to those familiar with the literature in this field: only 40% believed that vitamin therapy for hyperhomocysteinemia reduces the risk of stroke.

This is an important and costly blind spot in stroke prevention; it seems to arise from pronouncements by some misguided experts and a failure to carefully study the evidence. B vitamins are inexpensive and safe, and definitely do reduce the risk of stroke; they should be widely used for stroke prevention.

The issue is poorly understood, probably because it is complex. The early large trials of vitamin therapy to lower homocysteine showed no benefit, but there were reasons for that failure that can be understood. In the first large trial, the VISP (Vitamin Intervention for Stroke Prevention) trial,[4] patients were not randomized to vitamin vs placebo; they were randomized to high-dose B vitamins (25 mg of pyridoxine, 0.4 mg of cobalamin, and 2.5 mg of folic acid) vs low-dose vitamins (200 μg of pyridoxine, 6 μg of cobalamin, and 20 μg of folic acid). Note that the low dose of B_{12} was the recommended daily intake in the United States at the time, thus limiting the ability to show benefit of B_{12}. Furthermore, the study began at virtually the same time as folate fortification of the grain supply in North America, thus largely negating the benefit of folic acid. For ethical reasons, the executive committee (of which I was a member) was persuaded to treat all patients in both arms of the study with high doses of B_{12} if their baseline serum B_{12} level was low, thus negating the benefit of B_{12} in the very participants who would have benefited most.

In 2005, an analysis of the VISP trial excluded patients who were treated with B_{12} outside of their randomized assignment, and those with significant renal impairment (estimated glomerular filtration rate <46.18 mL/min/1.73 m^2; the 10th percentile).[5] In that analysis, patients who entered the trial with a serum B_{12} above the median and received high-dose vitamins had a 36% reduction of stroke/myocardial infarction/vascular death.

In 2006, in the same issue of the *New England Journal of Medicine*, 2 large trials were published. The NORVIT trial (Norwegian Vitamin Trial)[6] reported no benefit of B vitamins in stroke prevention, and even a slight increase in the risk of stroke with high-dose cyanocobalamin. The HOPE-2 trial[7] reported a 24% reduction of stroke with B vitamins, but the investigators, being cardiologists and therefore innocent of the cerebral circulation, concluded that this

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The author attests he is in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2024.06.003

TABLE 1 Dose of Cyanocobalamin, Renal Function, and Stroke Hazard With B Vitamins to Lower Homocysteine

Trial	Dose of Cyanocobalamin (mcg daily)	Serum Creatinine (μmol/L)		Stroke HR (95% CI)	*P* Value
		Active	Control		
DIVINe[16]	1000	141.4 (97.2)	123.8 (79.6)	6.6 (0.8-54.4)	0.08
VISP[18]	400	99.9 (55.7)	97.2 (47.7)	1.0 (0.8-1.3)	0.80
VITATOPS[18]	500	92.4 (40.3)	91.4 (34.6)	0.92 (0.81-1.06)	0.25
NORVIT[58]	400	91 (27)	91 (24)	0.83 (0.47-1.47)	0.52
HOPE 2[59]	1000	88.4 (26.5)	88.4 (26.5)	0.75 (0.59-0.97)	0.03
SU.Fol.OM3[20]	20	78 (70-88)	78 (0.69-88.0)	0.57 (0.33-0.97)	0.04

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DIVINe = Diabetic Intervention with Vitamins to Improve Nephropathy; eGFR = estimate glomerular filtration rate; HOPE-2 = Heart Outcomes Prevention Evaluation-2 Study; NORVIT = Norwegian Vitamin Trial; SU.Fol.OM3 = Supplémentation en Folates et Omega-3; VISP = Vitamin Intervention for Stroke Prevention trial; VITATOPS = Vitamins to Prevent Stroke.

was a chance finding because the risk of myocardial infarction was not reduced.

In 2010, the French Su.Fol.OM3 trial[8] reported a 40% reduction of stroke with B vitamins; importantly, the dose of cyanocobalamin used was much lower than in the other trials (20 μg daily vs 400-1,000 μg daily in the other trials), and the renal function was much better than in the earlier trials (**Table 1**).

In 2011, Spence and Stampfer[9] proposed that the reason the early trials failed to show reduction of stroke was because of toxicity of cyanocobalamin.

Then in 2015, it became clear that B vitamins do reduce the risk of stroke, with the publication of the CSPPT (China Stroke Primary Prevention Trial).[10] Importantly, folate fortification of the grain supply did not prevail in China. Among 20,000 hypertensive patients followed for nearly 5 years, folic acid reduced the risk of stroke by 21%. The benefit was greater among patients at higher risk; among those with total cholesterol >200 mg/dL (5.71 mmol/L), the reduction of stroke was 31%,[11] and among those with tHcy >15 μmol/L and a low platelet count, stroke was reduced by 70% with folic acid.[12] As with any therapy, the benefit of B vitamin therapy to lower homocysteine is greater among patients at higher risk.[13]

Thus it is now clear that the reason the early trials did not show a benefit of B vitamins in stroke prevention was toxicity of cyanocobalamin among participants with renal failure. This was confirmed in a meta-analysis in which trials were stratified by renal function and dose of cyanocobalamin.[14] We should be using methylcobalamin or hydroxocobalamin instead of cyanocobalamin.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that he has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS cardiac biomarker, folate, homocysteine, subclinical myocardial injury, vitamin B_{12}