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## Homocysteine: Call off the funeral

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## Homocysteine Call Off the Funeral

J. David Spence, MD, FRCPC, FAHA

See related article, pages 456–460.

The authors of the much publicized though not yet published Norwegian Vitamin Study (NORVIT)<sup>1</sup> of vitamin therapy in coronary artery disease, are widely quoted as saying that vitamin therapy for lowering plasma total homocysteine (tHcy) was harmful, and that “homocysteine is dead.” However, the slides of their presentation<sup>1</sup> do not show the B<sub>12</sub> status of the participants, nor do they indicate whether B<sub>12</sub> injections were given to participants with low levels of B<sub>12</sub>. Commentators<sup>2</sup> have called NORVIT “the largest trial to date to test the hypothesis that folate supplementation reduces risk of cardiovascular disease,” but because there were 4 treatment arms in NORVIT, each with 900 participants, the number of patients randomized to folate/B<sub>12</sub> or folate/B<sub>12</sub>/B<sub>6</sub> was essentially the same as that in the Vitamin Intervention for Stroke Prevention (VISP) trial<sup>3</sup> (≈1800). They used a much higher dose of B<sub>6</sub> than other studies and cannot exclude the possibility that their results were driven by that choice. As did VISP, they also used a dose of B<sub>12</sub> that, as has recently become apparent, was too low for adequate absorption of B<sub>12</sub> in elderly subjects (discussed below).

In this issue of *Stroke*, a substudy of the Vitamins to Prevent Stroke (VITATOPS) trial<sup>4</sup> reports that in Singapore, treatment with 2.5 mg folic acid, 0.5 mg vitamin B<sub>12</sub>, and 25 mg B<sub>6</sub> reduced levels of tHcy by 3.8 μmol/L compared with placebo.<sup>5</sup> The authors also studied 2 polymorphism of methylene tetrahydrofolate reductase (MTHFR) and found that the *MTHFR C677T* genotype was an independent determinant of tHcy levels at baseline ( $P=0.005$ ), but *A1298C* was not ( $P=0.08$ ). The reduction of tHcy was similar among patients with the wild-type alleles as in those with the 2 polymorphisms and was similar to that observed in VITATOPS patients in Perth, Australia.<sup>6</sup> These findings indicate that VITATOPS should have sufficient power to adequately test the hypothesis that lowering of tHcy reduces cardiovascular risk.

The authors suggested that the null effect of the VISP trial,<sup>3</sup> in which the separation of tHcy between high-dose and low-dose vitamin groups was only 2 μmol/L, was attributable

to folate fortification of grain cereal products in North America. However, there was more to the issue.

Reflection on the result of the intention-to-treat analysis of VISP, in light of evidence that became available after VISP was initiated, suggested that in the era of folate fortification, which coincided with the initiation of VISP, vitamin B<sub>12</sub> became the key determinant of response to vitamin therapy. In VISP, we did not use a placebo control; we gave to both arms of the study a multiple vitamin containing the usual recommended daily intake (RDI) of many vitamins, with either a low dose or a high dose of folate, B<sub>6</sub>, and B<sub>12</sub>.<sup>7</sup> Unfortunately, it appears we gave too high a dose of B<sub>12</sub> in the low-dose vitamin arm of the study (6 mcg daily; at least the RDI, or by some lights, 3× the RDI), and too low a dose of B<sub>12</sub> (400mcg daily) for elderly patients in the high-dose arm. A dose-response study<sup>8</sup> published 5 years after the initiation of VISP showed that elderly patients with B<sub>12</sub> levels <221 pmol/L require 1000 μg daily for adequate absorption. In part, that high-dose requirement may be related to administration of vitamin tablets at times other than mealtimes, when intrinsic factor is released from gastric mucosa. Then, we inadvertently negated the effect of B<sub>12</sub> in our randomized treatment by giving injections of vitamin B<sub>12</sub>, for safety and ethical reasons, to patients in both arms of the study who had low levels of serum B<sub>12</sub>. Thus, we ensured that the very patients most likely to respond to B<sub>12</sub> were not receiving their randomized therapy. Therefore, in VISP, what we showed was essentially that 25 mg daily of vitamin B<sub>6</sub> was ineffective.

We therefore analyzed<sup>9</sup> the results of VISP for patients who were capable of showing a response by excluding patients with B<sub>12</sub> levels <250 pmol/L (meaning they would have received B<sub>12</sub> injections or had reduced capacity to absorb B<sub>12</sub>, those with B<sub>12</sub> levels >637 pmol/L (indicating they were probably taking supplements) and excluding patients with renal failure (because they are less responsive to vitamin therapy<sup>10</sup>). In the 2155 patients remaining, there was a significant 21% reduction of stroke/death/coronary events. When we stratified this subgroup at the median serum B<sub>12</sub> level at entry (322 pmol/L), it became apparent that the principal determinant of response to vitamin therapy was the ability to absorb adequate levels of B<sub>12</sub>. The participants who fared the best were those with higher baseline B<sub>12</sub> levels who received high-dose vitamins; the ones who fared the worst were those who came into the trial with lower levels of B<sub>12</sub> and received low-dose vitamins ( $P=0.03$  for stroke/coronary events;  $P=0.02$  for stroke/death/coronary events). Thus, B<sub>12</sub> status was a key determinant of response to vitamin therapy.

The disparate results of 2 trials of vitamin therapy for homocysteine in coronary angioplasty also suggest that B<sub>12</sub> is a key component of such treatment. Whereas Schnyder et al, who showed a reduction of restenosis<sup>11</sup> and events<sup>12</sup> with

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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vitamin therapy, used 400 mcg daily of B<sub>12</sub>, Lange et al,<sup>13</sup> who showed no effect of vitamin therapy, used only 40 mcg daily.

It is increasingly clear that in the elderly (who represent a large proportion of vascular patients), the key nutritional determinant of plasma homocysteine is vitamin B<sub>12</sub>, and the real problem is malabsorption of B<sub>12</sub>. Furthermore, it is inappropriate to define adequate levels of serum B<sub>12</sub> by the “normal” range (mean±2SD or variants of that definition) because when defined metabolically (by levels of B<sub>12</sub> below which methylmalonic acid is elevated), ≈20% of the elderly are B<sub>12</sub> deficient.<sup>14</sup> Thus, the “normal” range includes patients with B<sub>12</sub> deficiency. The threshold B<sub>12</sub> level below which methylmalonic acid levels begin to rise (thus defining physiologically inadequate B<sub>12</sub>) is 258 pmol/L; in Framingham, 40.5% of the elderly (versus 17.9% of younger subjects) had levels below that threshold.<sup>15</sup> It has therefore been suggested that instead of measuring serum B<sub>12</sub>, measurement of holotranscobalamin would be a more sensitive way of defining adequacy of B<sub>12</sub>.<sup>16</sup> Robertson et al showed that in the era since folate fortification, serum B<sub>12</sub> is strongly related to plasma tHcy and to carotid plaque area,<sup>17</sup> and Quinlivan et al<sup>18</sup> also showed that in the setting of folate fortification, B<sub>12</sub> becomes a key determinant of tHcy.

In addition to the increasingly apparent importance of B<sub>12</sub> in lowering of tHcy, it should be recognized that some patients unresponsive to folate/B<sub>6</sub>/B<sub>12</sub> may need the addition of betaine,<sup>19</sup> and in renal failure, the addition of thiols,<sup>10,20,21</sup> to achieve adequate reductions of tHcy. It is therefore time to stop calling vitamin intervention for lowering of tHcy “folate therapy”; it should be called “vitamin therapy.”

It appears very likely that to achieve adequate reductions of tHcy in elderly patients, we will need higher doses of B<sub>12</sub> than have been used in the past. We should also await the results of VITATOPS<sup>4</sup> and other trials before scheduling the funeral for homocysteine.

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KEY WORD: hyperhomocysteinemia