Homocysteine, vitamins, and coronary artery disease

Comprehensive review of the literature

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OBJECTIVE To summarize results of clinical trials investigating the role of homocysteine (tHcy) as a risk factor for coronary artery disease (CAD) and the role of vitamin therapy (folic acid and vitamins B₆ and B₁₂) in primary and secondary prevention of CAD.

QUALITY OF EVIDENCE MEDLINE was searched from January 1976 to January 1999 to locate cross-sectional, retrospective and prospective cohort studies and meta-analyses on CAD using the MeSH words homocysteine, folic acid, vitamins B₆ and B₁₂, and coronary artery or heart disease.

MAIN MESSAGE Elevated tHcy levels are prevalent; most retrospective and cross-sectional studies show an association with increased risk of CAD. Results from recent prospective studies are less consistent. Folic acid, alone or with vitamins B₆ and B₁₂, reduces tHcy concentrations in the blood. Results from ongoing randomized controlled trials could determine the effect of vitamins B₆ and B₁₂ and folic acid supplementation on CAD-related morbidity and mortality and could indicate whether routine supplementation with these vitamins should be advocated. Before mass screening for tHcy can be done, the tHcy assay must be standardized.

CONCLUSION The role of homocysteine and vitamins B₆ and B₁₂ in managing CAD is unclear. Routine screening is not recommended.

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Cet article a fait l'objet d'une évaluation externe.
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C

onventional risk factors for coronary artery disease (CAD) include smoking, hypertension, hyperlipidemia, diabetes, and a family history. Family physicians should be aware of the discovery of new, potentially reversible, risk factors for CAD. Elevated serum levels of the amino acid homocysteine (tHcy) is one such factor.

Because this is a topic of increasing discussion in our medical community, this paper will review the medical literature to determine criteria for and prevalence of hyperhomocysteinemia in the general population; how tHcy serum levels are measured in the laboratory; how tHcy is metabolized, causes for elevated levels, and putative atherogenic role; results from retrospective and case-control studies and prospective cohort studies that do or do not support tHcy as an independent risk factor for CAD; the association between dietary intake and serum levels of folic acid, vitamin B6, and B12, and risk of CAD; and whether good evidence supports use of vitamin supplementation for primary or secondary prevention of CAD.

Quality of evidence

A MEDLINE search of English-language literature from January 1976 to January 1999 revealed 17 retrospective (case-control, cross-sectional) studies,1-17 one meta-analysis (based on studies completed before 1995),18 and eight prospective studies supporting tHcy as a risk factor for CAD.19-26 One of the supportive prospective studies, when extended by 2.5 years, however, no longer showed a statistically significant association between tHcy and incidence of CAD.27

More recently, results from four large prospective cohort studies also did not demonstrate a significant association between tHcy concentration and increased risk of CAD.28-31 Plasma vitamins B6 and B12 and folic acid are strong correlates of tHcy;12,16,18,32-34 the literature is not entirely consistent, but does suggest that folic acid and vitamin B6 and B12 concentrations in blood are associated positively with CAD occurrence.12,18,27,32-34 Results from five prospective epidemiologic studies showed low dietary folic acid and vitamin B6 and B12, or low serum folic acid to be associated with increased incidence of CAD.27,31 Twelve intervention studies showed notable decreases in tHcy levels after administration of folic acid with or without vitamins B6 and B12.45-55 Several prospective, double-blinded studies examining the effect of vitamin supplementation on morbidity and mortality of patients with CAD are currently under way.56

Main findings

Prevalence of hyperhomocysteinemia. Normal tHcy levels range from 5 to 15 µmol/L in fasting patients.40,43 Hyperhomocysteinemia is defined as any value above the 95th percentile or more than two standard deviations above the mean values obtained from healthy, fasting control subjects. Elevated tHcy levels are classified as moderate (15 to 30 µmol/L), intermediate (>30 to 100 µmol/L), or severe (>100 µmol/L) based on fasting blood samples. Using this definition of hyperhomocysteinemia, its prevalence in the general population is 5%.57 Between 13% and 47% of people with symptomatic atherosclerotic disease, however, have been reported to have hyperhomocysteinemia.55

Measurement of plasma tHcy levels. About 80% of total tHcy in blood is protein bound by disulfide linkage.58 Free tHcy is variable, but tHcy frozen immediately or centrifuged within 2 hours of collection (tHcy levels may increase secondary to the export of homocysteine from red and white blood cells) remains constant.59 Studies have not definitively established tHcy reference standards by age and sex, although these variables are known to influence tHcy levels, with higher tHcy concentrations in men and older people.60

Among patients with vitamin B12 deficiency, tHcy levels are generally higher than 23 µmol/L; confirmation might require serum methylmalonic acid assay.61 A single measurement of tHcy after fasting appears to be the most cost-effective method and has recently been offered in Canada at a cost of about $35 per assay. Testing for tHcy should always be done after fasting; efforts are under way to standardize testing methods.

How homocysteine works. Homocysteine is an amino acid formed as a result of metabolism of sulfuric methionine supplied from dietary proteins (eg, yellow and green leafy vegetables, grains, poultry, and meats). A simplification of tHcy metabolism is summarized in Figure 1. Several disease states and medications have been shown to elevate tHcy levels, and this elevation could lead to CAD if undetected (Table 1).

Nutrition: Researchers have suggested that up to two thirds of all hyperhomocysteinemia is attributable to

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Deficiencies of one or more B vitamins. Homocysteine levels can be markedly elevated with deficiencies of the essential cofactor vitamin B12 or the cosubstrate folic acid. An inverse relationship has been found to exist with plasma vitamins B6 and B12 and folic acid in relation to plasma tHcy levels in normal subjects.

Disease states: Markedly elevated tHcy levels have been reported in association with acute lymphoblastic leukemia; they decrease dramatically after chemotherapy. Moderately elevated tHcy levels have been found in patients with breast, ovarian, and pancreatic cancer. In patients with chronic renal failure, plasma tHcy levels can be two to four times normal, but they decrease with dialysis. A positive correlation exists between fasting tHcy and serum creatinine levels. Increases in tHcy levels during chronic renal failure might be due to impaired metabolism rather than excretion. The observed acceleration of atherosclerosis during end-stage renal disease could be due to elevated tHcy concentrations.

Hyperhomocysteinemia has been found in hypothyroid patients, suggesting an explanation for the observed higher incidence of vascular disease in hypothyroid patients. Hyperhomocysteinemia has also been reported in patients with pernicious anemia. Elevations in plasma tHcy levels are useful in diagnosing this disorder.

Drugs: Several drugs increase plasma tHcy levels: methotrexate, phenytoin, carbamazepine, and nitrous oxide. Methotrexate depletes folic acid, the cosubstrate for methionine synthase, and causes an increase in tHcy levels. Both phenytoin and carbamazepine interfere with folic acid metabolism, causing mild hyperhomocysteinemia. Nitrous oxide inactivates vitamin B12-dependent methionine synthase and is known to elevate tHcy levels. Smoking is associated with a proportional increase in plasma tHcy levels, particularly in older men who smoke 20 or more cigarettes a day.

Genetic causes: Cystathionine β-synthase deficiency is the most common genetic cause of hyperhomocysteinemia. Heterozygotes for this disorder have tHcy levels in the range of 20 to 40 µmol/L. Congenital hyperhomocystinuria, the homozygous form of the disease, can be associated with fasting levels of tHcy of up to 400 µmol/L, but this form of cystathionine β-synthase deficiency is rare (one in 20,000 births). About 50% of patients with untreated hyperhomocystinuria will have a thromboembolic event before age 30. A thermolabile variant of 5,10-methylenetetrahydrofolate reductase, caused by a point mutation (C677T) in the coding region for the folate binding site, has been found in 38% of French Canadians and 5% to 15% of the general Canadian population. This variant of the 5,10-methylenetetrahydrofolate reductase gene is not a significant independent risk factor for CAD. Those who are homozygous for this mutation, however, might be at increased risk of vascular disease.

Toxicity theory: It has been postulated that tHcy increases risk of CAD through direct toxicity to endothelial cells, increased coagulability, elevated triglyceride levels, and oxygen free radical production, which leads to lower endothelial reactivity with stimulation of smooth muscle cell proliferation (Figure 1).

Cross-sectional and retrospective case-control studies. Some evidence indicates tHcy is an independent risk factor for CAD. A meta-analysis based on 27 observational studies from 1976 to 1995 estimated that 10% of the United States population’s CAD risk could be attributed to elevated tHcy levels.
The odds ratio (OR) for CAD of a 5-µmol/L tHcy increment was 1.6 (95% confidence interval [CI] 1.4 to 1.7) for men and 1.8 (95% CI 1.3 to 1.9) for women. The authors concluded that a 5-µmol/L increase in tHcy raised CAD risk by as much as a 0.5-µmol/L increase in cholesterol.18 The summary estimate for homocysteine as a risk factor for CAD was determined in this meta-analysis to be 1.7 (95% CI 1.5 to 1.9).18 Since this meta-analysis, three more retrospective studies have provided evidence to support elevated tHcy levels increasing risk of CAD15-17.

Other evidence suggests tHcy is not an independent risk factor. Two smaller studies (one cross-sectional, one case-control)79,80 did not show increased risk of CAD with elevated tHcy levels. These results were later dismissed due to inadequate sample size and erroneous methods of measuring tHcy levels.

Prospective studies. Some evidence indicates tHcy is an independent risk factor for CAD. Eight prospective cohort studies have reported statistically significant positive associations between elevated tHcy levels and risk of CAD.19-26 One study reported a relative risk of 1.41 (95% CI 1.16 to 1.71) for every 4-µmol/L increase in serum tHcy.20 The study by Nygard et al21 used patients with angiographically proven heart disease who were followed for a median of 4.6 years. This cohort showed a strong, graded association between tHcy concentration and overall mortality.23 This association was strongest for tHcy levels above 15 µmol/L, with an adjusted mortality OR of 1.6 for patients with tHcy concentrations of 15 µmol/L compared with patients with levels of 10 µmol/L. After 4 years, only 3.8% of patients with tHcy <9 µmol/L had died compared with 24.7% of those with tHcy >15 µmol/L (mortality OR 4.5; 95% CI 1.2 to 16.6) for patients with the highest tHcy levels compared with the lowest. Similarly, after 5 years of follow up the Physician’s Health Study reported an adjusted relative risk of fatal or non-fatal MI of 3.4 (CI 1.3 to 8.8; P = 0.01) (Table 319,26,28).

Other evidence suggests tHcy is not an independent risk factor. In contrast to the results discussed above, recent studies have failed to demonstrate a significant association between tHcy concentration and incidence of CAD.27-31 (Table 427-31). Five reports of four large cohorts followed prospectively do not support a cause-and-effect association between elevated tHcy levels and risk of CAD.27-31 In particular, when the Physician’s Health Study was extended by 2.5 years, results no longer showed a statistically significant association between tHcy levels and incidence of CAD.27

Similarly, the Multiple Risk Factor Intervention Trial29 and the Atherosclerosis Risk in Communities (ARIC) Study30 did not find a significant association between elevated tHcy levels and fatal or non-fatal CAD. Three of the five studies showed a trend toward increased risk of CAD with elevations in tHcy.27,28,30 A significant association might not have been reached because the three studies did not compare events (ie, fatal or non-fatal myocardial infarctions [MIs]) in people at extreme ends of tHcy plasma concentration as the studies that supported tHcy as a risk factor for CAD did. One of these studies suggests, however, that tHcy is a consequence, not a cause, of CAD.28 Among patients with CAD, elevated tHcy levels strongly predict poor outcome,77 suggesting that tHcy reflects the severity of CAD and perhaps the risk of thrombosis. Among smokers, using an adjusted dose-response relationship, elevated levels of tHcy are not associated with increased mortality.69

Dietary intake and serum levels of folic acid and vitamins B6 and B12. Although not entirely consistent, most retrospective cross-sectional and prospective cohort studies show a positive and dose-dependent association between serum levels or dietary intake of folic acid and vitamins B6 and B12 and risk of CAD.12,18,27,32-34,36-44 Changes in tHcy levels might simply be an epiphenomenon and might, in fact, have no direct effect on risk of developing CAD. A recent prospective epidemiologic study among 80 082 women enrolled in the Nurse’s Health Study followed for...
Table 2. **Retrospective studies supporting homocysteine as a risk factor for coronary artery disease (CAD):** Summary risk estimate for CAD in references 1 to 17 is 1.7 (95% CI, 1.5 to 1.9) as determined by Boushey et al.\(^\text{18}\)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>CASES/ CONTROLS</th>
<th>SEX*</th>
<th>AGE (Y)†</th>
<th>DESIGN</th>
<th>MEAN TOTAL HOMOCYSTEINE LEVELS (µMOL/L) CASES/ CONTROLS (P FOR DIFFERENCE)</th>
<th>MAIN FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilcken and Wilcken(^1)</td>
<td>25/22</td>
<td>Men</td>
<td>&lt;50</td>
<td>Cross-sectional</td>
<td>NA/ NA</td>
<td></td>
</tr>
<tr>
<td>Murphy-Chutorian et al(^2)</td>
<td>99/39</td>
<td>Men</td>
<td>21-65</td>
<td>Cross-sectional</td>
<td>0.7/ 0.6</td>
<td></td>
</tr>
<tr>
<td>Kang et al(^3)</td>
<td>241/202</td>
<td>Men</td>
<td>&lt;69</td>
<td>Cross-sectional</td>
<td>5.5/ 4.3 (&lt;001)</td>
<td></td>
</tr>
<tr>
<td>Israelsson et al(^4)</td>
<td>21/36</td>
<td>Men</td>
<td>48-58</td>
<td>Population case control</td>
<td>16.4/ 13.5</td>
<td></td>
</tr>
<tr>
<td>Malinow et al(^5)</td>
<td>64/92 35/167 99/259</td>
<td>Men</td>
<td>Women</td>
<td>Cross-sectional</td>
<td>13.1/ 13.3 (&lt;05) 12.9/ 10.2 (&lt;05) NA</td>
<td></td>
</tr>
<tr>
<td>Genest et al(^6)</td>
<td>170/255</td>
<td>Men</td>
<td>&lt;60</td>
<td>Case control</td>
<td>13.7/ 10.9 (&lt;001)</td>
<td></td>
</tr>
<tr>
<td>Ubbink et al(^7)</td>
<td>163/195</td>
<td>Men</td>
<td>55</td>
<td>Case control</td>
<td>16.2/ 13.4</td>
<td></td>
</tr>
<tr>
<td>Clarke et al(^8)</td>
<td>60/27</td>
<td></td>
<td>&lt;55</td>
<td>Case control</td>
<td>18.7/ 13.4</td>
<td></td>
</tr>
<tr>
<td>Dudman et al(^9)</td>
<td>14/36 48/20 62/56</td>
<td>Women</td>
<td>Men</td>
<td>Case control</td>
<td>NA NA</td>
<td></td>
</tr>
<tr>
<td>Pancharuniti et al(^10)</td>
<td>101/108</td>
<td>Men</td>
<td>30-50</td>
<td>Population case control</td>
<td>13.5/ 11.9 (&lt;001)</td>
<td></td>
</tr>
<tr>
<td>Von Eckardstein et al(^11)</td>
<td>199/156</td>
<td>Men</td>
<td>36-65</td>
<td>Case control</td>
<td>8.9/ 7.8 (&lt;001)</td>
<td></td>
</tr>
<tr>
<td>Hopkins et al(^15)</td>
<td>304/231</td>
<td></td>
<td>62</td>
<td>Case control</td>
<td>13.1/ 10.1 M en: OR 13.8 (CI 3.5-55) Women: OR 12.8 (CI 2.0-82)(^\text{i})</td>
<td></td>
</tr>
<tr>
<td>Dalery et al(^16)</td>
<td>420/521</td>
<td></td>
<td>25-64</td>
<td>Case control</td>
<td>11.8 (&lt;001) / 8.6 (&lt;01) M en: P &lt;001 Women: P &lt;01</td>
<td></td>
</tr>
<tr>
<td>Robinson et al(^17)</td>
<td>162/155</td>
<td></td>
<td>38-68</td>
<td>Case control</td>
<td>14.6/ 10.6 (&lt;01)</td>
<td></td>
</tr>
<tr>
<td>Malinow et al(^13)</td>
<td>150/584</td>
<td></td>
<td>20-59</td>
<td>Case control</td>
<td>16.7/ 12.9 Irish arm: OR 3.4 (CI 1.6-7.2) French arm: OR 5.18 (CI 2.9-9.3)</td>
<td></td>
</tr>
<tr>
<td>Graham et al(^12)</td>
<td>750/800</td>
<td></td>
<td>48</td>
<td>Case control</td>
<td>11.3/ 9.7 RR 2.2 (CI 1.6-2.9)</td>
<td></td>
</tr>
</tbody>
</table>

CI—confidence interval; NA—not available; OR—odds ratio; RR—relative risk.

*Unless otherwise designated, includes both men and women.

†Unless otherwise specified, mean age of participants.

\(^\text{i}\)For tHcy levels >19 µmol/L vs <9 µmol/L.
Table 3. Prospective studies supporting homocysteine as a risk factor for coronary artery disease (CAD)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>CASES/ CONTROLS</th>
<th>SEX*</th>
<th>AGE (Y)†</th>
<th>MAIN OUTCOMES</th>
<th>MEAN TOTAL HOMOCYSTEINE LEVELS (µMOL/L) CASES/ CONTROLS</th>
<th>RR OR OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stampfer et al19</td>
<td>271/ 271</td>
<td>Men</td>
<td>40-84</td>
<td>Fatal/ non-fatal MI</td>
<td>11.1/ 10.5 (P &lt; .05)</td>
<td>3.4 (1.3-8.8)</td>
</tr>
<tr>
<td>Arnesen et al20</td>
<td>122/ 478</td>
<td></td>
<td>53</td>
<td>Fatal/ non-fatal CAD</td>
<td>12.7/ 11.3</td>
<td>1.41 (1.16-1.71)</td>
</tr>
<tr>
<td>Perry et al22</td>
<td>107/ 118</td>
<td>Men</td>
<td>12-61</td>
<td>Fatal/ non-fatal stroke</td>
<td>13.7/ 11.9</td>
<td>2.8 (1.3-5.9)</td>
</tr>
<tr>
<td>Petri et al25</td>
<td>60</td>
<td></td>
<td>35</td>
<td>Arterial thrombosis NA/ NA</td>
<td></td>
<td>3.49 (0.97-12.54)</td>
</tr>
<tr>
<td>Nygard et al23</td>
<td>478</td>
<td>Men</td>
<td>62</td>
<td>Fatal CAD</td>
<td>11.4/ NA</td>
<td>4.5 (1.22-16.6)</td>
</tr>
<tr>
<td></td>
<td>109</td>
<td>Women</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wald et al21</td>
<td>229/ 126</td>
<td>Men</td>
<td>35-64</td>
<td>Fatal CAD</td>
<td>&gt;15.2/ &lt;10.3</td>
<td>2.9 (2.04-4.1)</td>
</tr>
<tr>
<td>Stehouwer et al24</td>
<td>878/ 162</td>
<td>Men</td>
<td>64-84</td>
<td>MI</td>
<td>NA/ NA</td>
<td>1.81 (1.07-3.08)</td>
</tr>
<tr>
<td>Bots et al26</td>
<td>224/ 553</td>
<td>&gt;55</td>
<td>MI</td>
<td></td>
<td>17.3/ NA</td>
<td>2.43 (1.11-5.35)</td>
</tr>
</tbody>
</table>

CI—confidence interval; MI—myocardial infarction; NA—not available; OR—odds ratio; RR—relative risk.
*Unless otherwise designated, includes both men and women.
†Unless otherwise specified, mean age of participants.
‡Results no longer showed significant association of total homocysteine with incidence of CAD when was study extended by 2.5 years.28

Table 4. Prospective studies not supporting homocysteine as a risk factor for coronary artery disease (CAD)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>CASES/ CONTROLS</th>
<th>SEX*</th>
<th>AGE (Y)†</th>
<th>MAIN OUTCOMES</th>
<th>MEAN TOTAL HOMOCYSTEINE LEVELS (µMOL/L) CASES/ CONTROLS</th>
<th>RR OR OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfthan et al28</td>
<td>92/ 141</td>
<td>Men</td>
<td>40-64</td>
<td>Fatal/ non-fatal MI</td>
<td>9.8/ 9.8</td>
<td>1.05 (0.56-0.95)</td>
</tr>
<tr>
<td></td>
<td>99/ 128</td>
<td>Women</td>
<td></td>
<td></td>
<td>9.4/ 9.3</td>
<td>1.22 (0.66-0.78)</td>
</tr>
<tr>
<td>Chasan-Taber et al27</td>
<td>333/ 333</td>
<td>Men</td>
<td>40-84</td>
<td>Fatal/ non-fatal MI</td>
<td>5.0/ 5.2</td>
<td>1.7 (0.9-3.3)</td>
</tr>
<tr>
<td>Evans et al29</td>
<td>93/ 186</td>
<td>Men</td>
<td>35-57</td>
<td>Non-fatal MI, CAD, death</td>
<td>12.6/ 13.1</td>
<td>0.82 (0.55-1.54)</td>
</tr>
<tr>
<td></td>
<td>147/ 286</td>
<td></td>
<td></td>
<td></td>
<td>12.8/ 12.7</td>
<td></td>
</tr>
<tr>
<td>Folsom et al30</td>
<td>232/ 537</td>
<td></td>
<td>45-64</td>
<td>All CAD events</td>
<td>8.86/ 8.53</td>
<td>1.28 (0.5-3.2)</td>
</tr>
<tr>
<td>Verhoeof et al31</td>
<td>109/ 427</td>
<td>Men</td>
<td>40-84</td>
<td>New angina/ CABG</td>
<td>10.9/ 10.4</td>
<td>1.0 (0.4-2.4)</td>
</tr>
</tbody>
</table>

CABG—coronary artery bypass grafting; CI—confidence interval; MI—myocardial infarction; OR—odds ratio; RR—relative risk.
*Unless otherwise designated, includes both men and women.
†Non-fatal MI cases.
‡Deaths from coronary heart disease (CHD).
§Composed of 146 definite or probable MIs, 19 silent MIs, 30 definite fatal CHDs, and 37 revascularization procedures.
14 years examined the relation between intake of folic acid and vitamin B₆ and risk of CAD. A large portion of this study group had insufficient intake of vitamin B₆ and folic acid to prevent CAD, in agreement with the Framingham Heart Study. Women with the lowest intake of folic acid and vitamin B₆ had the greatest risk of mortality and MI. In the large prospective ARIC study, only plasma vitamin B₆ was associated with incidence of CAD after accounting for other risk factors. The relative risk (RR) for highest versus lowest quintile of vitamin B₆ was 0.28 (95% CI 0.1 to 0.7). Interestingly, arterial lesions have been seen in animals raised on vitamin B₆-deficient diets. A summary of the main prospective studies supporting the role of folic acid and vitamins B₆ and B₁₂ in risk of CAD are shown in Table 5.

**Vitamin supplementation for preventing CAD.** Several studies have shown substantial decreases in tHcy levels when patients add folic acid, with or without vitamins B₆ and B₁₂, to their diets. According to the Nurse’s Health Study, risk of CAD was reduced among women who regularly used multiple vitamins (RR 0.76; 95% CI 0.65 to 0.90). Maximum benefit was found among women in the highest quintile of both folic acid and vitamin B₆ intake (RR 0.57; 95% CI 0.40 to 0.82). This finding is consistent with the independent effects of these vitamins in lowering tHcy levels, suggesting that maximum benefit can be obtained with optimal levels of both vitamins.

The association between dietary folic acid intake and tHcy levels appears to reach a plateau beyond which tHcy levels remain stable. Existence of a plateau is supported by studies showing that tHcy levels did not decrease any more after 6 weeks of treatment with 1000 µg of folic acid, 0.4 mg of vitamin B₁₂, and 12.2 mg of vitamin B₆ when twice these amounts were given. The minimum daily dose of folic acid that has maximal efficacy in decreasing plasma tHcy levels is about 0.4 mg. A recent meta-analysis summarizing the effects of vitamin therapy on tHcy levels showed that folic acid alone at 0.5 to 5.0 mg/d was accompanied by a 25% reduction in tHcy levels (CI 23% to 28%).

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**Table 5. Prospective studies of folate, vitamins B₆ and B₁₂, and cardiovascular risk**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>AGE (Y)</th>
<th>PARTICIPANTS</th>
<th>DESIGN</th>
<th>MEAN FOLLOW UP (Y)</th>
<th>MAIN RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Bree et al</td>
<td>35-79</td>
<td>165 men and women who died of CAD</td>
<td>Prospective cohort nested case-control</td>
<td>15</td>
<td>RR 1.69 for lowest vs highest quarters of folate level</td>
</tr>
<tr>
<td>Verhoef et al</td>
<td>40-84</td>
<td>333 men after MI</td>
<td>Prospective cohort nested case-control</td>
<td>7.5</td>
<td>RR 1.4 (CI 0.9-2.3) for lowest vs highest fifths of folate level; RR 1.5 (CI 1.0-2.2) for lowest vs highest fifths of vitamin B₆ level</td>
</tr>
<tr>
<td>Morrison et al</td>
<td>45-64</td>
<td>232 men and women with fatal and non-fatal CAD</td>
<td>Prospective cohort nested case-control</td>
<td>3.3</td>
<td>RR 0.66 (CI 0.3-1.5) for highest vs lowest fifths of folate level; RR 0.28 (CI 0.1-0.7) for highest vs lowest fifths of vitamin B₆ level</td>
</tr>
<tr>
<td>Giles et al</td>
<td>35-74</td>
<td>98 men and women with ischemic stroke</td>
<td>Prospective cohort nested case-control</td>
<td>13</td>
<td>RR 1.37 (CI 0.82-2.29) for serum folate level &lt;9.2 µmol/L vs ≥9.2 µmol/L</td>
</tr>
<tr>
<td>Rimm et al</td>
<td>30-55</td>
<td>658 women with non-fatal MI and CAD death</td>
<td>Prospective cohort nested case-control</td>
<td>14</td>
<td>RR 0.69 (CI 0.55-0.87) for highest vs lowest fifths of folate level; RR 0.67 (CI 0.53-0.85) for highest vs lowest fifths of vitamin B₆ level</td>
</tr>
</tbody>
</table>

CAD—coronary artery disease; CI—confidence interval; MI—myocardial infarction; RR—relative risk.
Normalization of plasma tHcy levels occurred 2 to 6 weeks after initiation of folic acid therapy regardless of the reason for the elevated tHcy. Addition of 0.5 mg/d of vitamin B₁₂ to folic acid was associated with an additional 7% drop in tHcy levels, but addition of 16.5 mg/d of vitamin B₆ did not further lower them. The authors acknowledge, however, that these results might be due to their exclusion of studies using one version of the tHcy assay, the results of which might depend more on vitamin B₆.⁸⁷

Canada has recently followed the lead of the United States Food and Drug Administration and has begun supplementing cereal and flour products with 140 µg of folic acid per 100 g of flour. It remains to be seen whether fortifying cereal or flour products with folic acid has any effect on tHcy levels and ultimately CAD risk in the general population.

A rare but potentially serious side effect of folic acid supplementation is subacute combined degeneration of the spinal cord in people with subclinical vitamin B₁₂ deficiency. To avoid this complication, physicians should rule out vitamin B₁₂ deficiency before therapy; 400 to 1000 µg/d of vitamin B₁₂ is suggested. The doses of vitamin B₆ used to treat mildly or moderately elevated total plasma tHcy levels are too low (25 to 50 mg/d) to induce sensory neuropathy.

Before vitamin therapy can be approved for primary and secondary prevention of CAD, results from ongoing randomized clinical trials evaluating the effect of vitamin therapy on patient morbidity and mortality must be analyzed. The trials looking specifically at MI as an end point include the Cambridge Heart Antioxidant Study (CHAOS-2), the Norwegian Study of Homocysteine Lowering with B-Vitamins in Myocardial Infarction (NORVIT), and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).⁵⁶

Conclusion
Most retrospective studies support an association between elevated tHcy levels and increased risk of CAD, but data from prospective studies are less consistent. Results from large randomized controlled trials are needed to better clarify the relationships among tHcy, folic acid, B vitamins, and risk of CAD.

Adding 0.5 mg/d of folic acid alone can reduce basal tHcy levels by about 25% adding 0.5 mg/d of vitamin B₁₂ to the folic acid further reduces levels by 7%. Most of the literature supports combining vitamin B₆, about 25 to 50 mg/d, with folic acid and vitamin B₁₂. A large randomized controlled trial with clear end points in terms of reducing CAD morbidity and mortality with vitamin therapy would provide the best evidence on which to base our preventive interventions. Until we know the effect of vitamin supplementation on primary and secondary prevention of CAD, we have no evidence upon which to recommend testing any patient’s tHcy levels. Also, before routine testing can be advocated, the assay must be standardized.

Finally, the effect of vitamin therapy on clinical outcome must be of proven clinical benefit. In the meantime, family physicians are urged to continue to...
Homocysteine, vitamins, and coronary artery disease

detect and actively manage traditional risk factors for CAD, including promotion of a well-balanced and nutritious diet.

References


57. McCully KS. Homocysteine and vascular disease.


