Homocysteine as a risk factor for cardiovascular disease: should we (still) worry about it?

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Summary

Cardiovascular disease (CVD) is the leading cause of death worldwide. CVD is causally related to “classical” risk factors such as elevated blood pressure, cholesterol, or glucose level and smoking. A causal role in the development of CVD is also suggested for numerous other factors, including an elevated plasma homocysteine concentration. Variation of homocysteinaemia is mainly due to genetic mutations and/or vitamin deficiency. The homocysteine concentration can be lowered with folate. Vitamin supplementation has thus been proposed in individuals with hyperhomocysteinaemia in order to reduce their CVD risk. On the other hand, population-based studies show little or no association between moderate hyperhomocysteinaemia and CVD risk. Nor has any randomised clinical trial clearly proven the efficacy of lowering the homocysteine concentration as a means of lowering the incidence of CVD. Hence at present it is inappropriate to recommend screening and treatment of hyperhomocysteinaemia in asymptomatic persons with or without other CVD risk. Until new evidence is available, clinicians should focus on better control of the “classical” risk factors for CVD.

Key words: homocysteine; cardiovascular disease; risk factor; treatment; screening

Introduction

Smoking, high blood pressure, elevated serum cholesterol and elevated serum glucose are major modifiable risk factors for cardiovascular disease (CVD) [1]. Numerous other risk factors – or risk markers for CVD – have been identified, including homocysteine [1]. The aetiological role of these “new” risk factors/markers in the development of CVD is fiercely debated. How far these factors add value to the “classical” risk factors for the prediction or the prevention of CVD morbidity/mortality risk is uncertain. Others argue that only 50% of CVD can be explained by “classical” risk factors, and that “new” risk factors could significantly boost CVD predictive power [2]. However, this claim has been widely criticised [3, 4] by authors who show that up to three quarters of coronary heart disease (CHD) events, if not more, could be attributed to “classical” risk factors [5, 6]. To be considered clinically relevant, a risk factor should add significantly to the predictive value of “classical” risk factors for CVD and its treatment should be associated with a proven reduction in CVD risk. Alternatively, a new risk factor can also be meaningful when it is easier (or cheaper) to obtain than a classical risk factor.

Numerous observational studies have shown that high homocysteine concentrations are associated with a heightened risk of CVD [7–10]. Since homocysteine levels can be reduced with B vitamins, some authors recommend treatment when the homocysteine concentration exceeds 10 μmol/L [11–16]. Typically, folate was proposed as part of the debated “polypill”, a combination of various drugs (i.e. three blood pressure lowering drugs, a statin, aspirin, and folate), which would reduce the risk of ischaemic heart disease events and strokes by more than 80% in persons presenting with CVD or aged 55 years or more [17]. Another proposed strategy is systematic screening for hyperhomocysteinaemia and, if necessary, correction by vitamin supplementation [14–16, 18]. However, to qualify as a screening tool, a risk factor should be strongly and causally associated with the target disease [19], and many authors doubt whether such a relationship between homocysteine and CVD exists [7, 20–25].

We reviewed the available evidence concerning the association between serum homocysteine and CVD, with the objective of discussing the pertinence of screening, treatment, and prevention of
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hyperhomocysteaemia in a general and/or in a selected clinical population. This review does not refer to supplementation of folic acid to reduce the risk of neural tube defects, which must be discussed separately [26].

Homocysteine metabolism

Homocysteine, a sulphur-containing amino acid, is an intermediate product in the normal biosynthesis of the amino acids methionine and cysteine. Homocysteine is predominantly metabolised via two pathways (figure 1). The enzyme N5, N10-methylenetetrahydrofolate reductase (MTHFR) [24] converts homocysteine to methionine. When MTHFR activity is low, homocysteine transformation to methionine is impaired and homocysteine accumulates in the blood. The activity of MTHFR is strongly dependent on the presence of the two vitamins folate (vitamin B9) and cobalamin (vitamin B12). The conversion of homocysteine to cysteine is catalysed by cystathionine-β-synthase (C’S), an enzyme with pyridoxine (vitamin B6) as an essential cofactor [24]. Similarly to MTHFR, low C’S activity translates into increased homocysteine concentrations.

Possible causes of hyperhomocysteinaemia

There are two types of hyperhomocysteinaemia: (1) rare, severe forms are due to major genetic mutations of the enzymes implicated in homocysteine metabolism; (2) the more common forms result in moderately elevated homocysteine levels related to a pathogenesis that includes genetic and environmental factors.

The homozygous mutation of C’S can cause severe hyperhomocysteinaemia with homocysteine concentrations of up to 40-fold normal levels [24]. This disease occurs in approximately one of 100,000 live births [27]. When untreated, a vascular event (stroke, myocardial infarction, other thromboembolic complication) occurs in about half of these patients before the age of 30 [28]. Another cause of rare, genetically mediated severe hyperhomocysteinaemia is due to homozygous mutations of MTHFR [24, 29]. Similarly, persons with these mutations have premature CVD, and vitamin treatment may reduce the risk of CVD in patients with some enzyme function [24].

Some genetic mutations may only mildly impair homocysteine metabolism. Among the known mutations of MTHFR the two best characterised are A1298C and C677T (missense mutations) [30]. Only C677T may lead to increased homocysteine levels. This point mutation (C-to-T substitution at nucleotide 677) in the gene for MTHFR is associated with a thermolabile MTHFR variant having approx. half-normal activity. Together with a low folate intake, patients with this mutation may have moderate or intermediate hyperhomocysteinaemia [24, 31]. MTHFR mutations can be found in about 30% of individuals with moderately increased homocysteine levels, and in 70% of subjects with intermediate hyperhomocysteinaemia [21]. Transcobalamin is a protein which is required for vitamin B12 uptake and metabolism. A common genetic polymorphism of transcobalamin (missense mutation: TC 776CÆG) can also be responsible for increased homocysteine levels [32].

Low intake of folate, vitamin B12, and to a lesser extent vitamin B6 are associated with increased homocysteine levels independently of any genetic mutation [18, 24]. In addition, several diseases such as renal and thyroid dysfunction, cancer, psoriasis, and diabetes may be associated with moderately elevated homocysteine concentrations [18, 24]. Finally, various drugs, alcohol, tobacco, and coffee consumption, as well as older age and menopause, are associated with high homocysteine levels [18, 24] (table 1).
Mean homocysteine levels and the prevalence of hyperhomocysteinaemia vary significantly between populations, and probably depend on age, diet, and genetic background. Also, the definition of hyperhomocysteinaemia differs between studies [33–35]. Moreover, differences in folate intake, in particular food fortification with folate, may also add to the variations between populations. Most studies indicate prevalences of hyperhomocysteinaemia above 10% in developed countries (table 2). Currently, no data are available for Switzerland.

**Table 1**

<table>
<thead>
<tr>
<th>Blood concentration</th>
<th>Moderate hyperhomocysteinaemia</th>
<th>Intermediate hyperhomocysteinaemia</th>
<th>Severe hyperhomocysteinaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–30 μmol/L</td>
<td></td>
<td>31–100 μmol/L</td>
<td>&gt;100 μmol/L</td>
</tr>
<tr>
<td>Mutations and polymorphisms</td>
<td>Homozygous mutation (677C→T) of methylenetetrahydrofolate reductase (MTHFR)</td>
<td>Homozygous mutation of (677C→T) MTHFR</td>
<td></td>
</tr>
<tr>
<td>Heterozygous mutation (I278T and G307S) of cystathionine β-synthase (CβS)</td>
<td>Mutations (e.g. P1297L) leading to vitamin B12 deficiency</td>
<td>Homozygous mutation (I278T and G307S) of CβS</td>
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</tr>
<tr>
<td>Mutation (TC 776C→G) of transcobalamin</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>Deficiencies in folate, Vitamin B12, B6, cholin, serin</td>
<td>Deficiencies in folate, Vitamin B12, B6, cholin, serin</td>
<td>Severe deficiencies in folate, Vitamin B12, B6, cholin, serin</td>
</tr>
<tr>
<td></td>
<td>Increased intake in methionine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diseases</td>
<td>Renal impairment</td>
<td></td>
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<tr>
<td></td>
<td>Pernicious anaemia</td>
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<td></td>
<td>Hypothyroidism</td>
<td></td>
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<td></td>
<td>Various cancers</td>
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<tr>
<td></td>
<td>Psoriasis</td>
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<td></td>
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<tr>
<td></td>
<td>Diabetes</td>
<td></td>
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<tr>
<td>Drugs</td>
<td>Folate antagonists</td>
<td></td>
<td>Folate antagonists</td>
</tr>
<tr>
<td></td>
<td>Vitamin B6 antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Tobacco</td>
<td></td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coffee</td>
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<tr>
<td></td>
<td>Menopause</td>
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<td></td>
<td>Male sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Old age</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Prevalence of hyperhomocysteinaemia**

Mean homocysteine levels and the prevalence of hyperhomocysteinaemia vary significantly between populations, and probably depend on age, diet, and genetic background. Also, the definition of hyperhomocysteinaemia differs between studies [33–35]. Moreover, differences in folate intake, in particular food fortification with folate, may also add to the variations between populations. Most studies indicate prevalences of hyperhomocysteinaemia above 10% in developed countries (table 2). Currently, no data are available for Switzerland.

**Homocysteine and the risk of vascular and other diseases**

In 1969, McCully described premature atherosclerosis in children with homocysteinuria [36]. Homocysteinuria is a rare autosomal recessive condition marked by major alterations in the activity of MTHFR, CβS, and an enzyme implicated in vitamin B12 metabolism, resulting in markedly increased homocysteine levels [36]. In 1976, Wilcken found higher homocysteine levels due to abnormalities in methionine metabolism in coronary artery disease patients compared to healthy controls (normal coronaryography) [37]. Meanwhile, a substantial amount of data from case-control and cohort studies has been gathered which supports a relationship between moderately elevated homocysteine levels and the risk of CVD (coronary heart, cerebrovascular, and peripheral artery diseases) [7–10]. More recently, hyperhomocysteinaemia has been shown to be associated with a higher risk of venous thrombosis [38, 39]. Other studies suggest that elevated homocysteine concentrations may be associated with alterations in mental health [40], e.g. cognitive impairment [41, 42], dementia [43], depression [44, 45] or Alzheimer’s [43, 46, 47] and Parkinson’s disease [48].

In vitro studies indicate that homocysteine may have a harmful effect on endothelial cells, increase coagulability, and have a proliferative effect on smooth muscle cells [49–54]. However, homocysteine doses given in many in vitro studies (up to 200 μmol and more) far exceed pathological homocysteine levels in humans [50–52]. Another
point is related to the prooxidative properties of homocysteine which may induce oxidative stress. On the one hand, this leads to impaired synthesis of nitric oxide (NO, a potent vasodilator) and other vasoactive substances, resulting in endothelial dysfunction [52, 55–57]. On the other hand, homocysteine-induced oxidative stress favours proatherogenic transformation of lipoproteins [57] and induces production of inflammatory factors such as TNF-alpha [58], thus accelerating atherosclerosis in animal models [58, 59]. In mice with a genetic deficiency of CBS, hyperhomocysteinaemia was associated with impaired endothelial function [60] and abnormal lipid metabolism [61]. Abnormal lipid deposition in the aorta was observed in mice with mutation of the MTHFR gene [62]. Finally, increased homocysteine levels could also cause an imbalance in coagulation/thrombolytic factors towards a prothrombotic state [63, 64].

Homocysteine can be lowered by supplementation with folate, vitamin B<sub>6</sub>, and B<sub>12</sub> [65]. Supplementation with these vitamins is inexpensive, safe, and effective in normalising hyperhomocysteinaemia [66–68]. In patients with markedly increased homocysteine levels, vitamin treatment was associated with a decrease in CVD risk in a controlled trial [69]. In individuals with moderate hyperhomocysteinaemia, vitamin supplementation may lower homocysteine concentrations [70, 71] when daily folate intake exceeds 400 μg/day [11]. Some authors suggest that such a correction of elevated homocysteine levels could reduce the relative risk of CVD by approximately 10% in the general population, and up to 25% in high risk groups [7, 72]. Foods rich in folate include green leafy vegetables, wheat germ, and sprouts, but beans, citrus fruits, and liver are also good sources. It is difficult to achieve an intake of ≥400 μg/day of folate with a normal diet. For instance, this would require eating 560 g of broccoli or 1.2 kilo of oranges daily [73], suggesting that vitamin supplementation or food fortification with folate (e.g. flour) would be necessary to obtain the appropriate daily supply [11, 66, 67, 74]. Voluntary fortification in an adult Australian population was associated with a 38% increase in mean serum folate and a 21% decrease in mean homocysteine [68], corresponding to a supposed reduction in ischaemic heart disease (IHD) and stroke of 13% and 20% respectively [68].

### Table 2

Mean homocysteine levels and prevalence of hyperhomocysteinaemia in different populations.

<table>
<thead>
<tr>
<th>Region</th>
<th>Publication year</th>
<th>Sample size</th>
<th>Age of participants (years)</th>
<th>Mean homocysteine levels</th>
<th>Cut-off for hyperhomocysteinaemia</th>
<th>Prevalence of hyperhomocysteinaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe [35]</td>
<td>2005</td>
<td>25,489</td>
<td>&gt;20</td>
<td>M: 12.4 μmol/L (range: 9.0–15.9), F: 10.6 μmol/L (range: 8.7–15.3)</td>
<td>Total homocysteinaemia &gt;15 μmol/L</td>
<td>11%</td>
</tr>
<tr>
<td>United States [33]</td>
<td>2000</td>
<td>2,491</td>
<td>60–95</td>
<td>10.1 μmol/L (before food fortification with folate) 9.4 μmol/L (after food fortification with folate)</td>
<td>Total homocysteinaemia &gt;13 μmol/L</td>
<td>18.7% (before food fortification with folate) 9.8% (after food fortification with folate)</td>
</tr>
<tr>
<td>Australia (Sydney) [105]</td>
<td>2004</td>
<td>2,963</td>
<td>≥50</td>
<td>n. a.</td>
<td>Total homocysteinaemia &gt;15 μmol/L</td>
<td>M: 20.8%, F: 13.7%</td>
</tr>
<tr>
<td>Iran (Tehran) [106]</td>
<td>2006</td>
<td>1,214</td>
<td>25–64</td>
<td>M: 19.02 μmol/L, F: 14.05 μmol/L</td>
<td>Total homocysteinaemia &gt;15 μmol/L</td>
<td>M: 73.1%, F: 41.07%</td>
</tr>
<tr>
<td>Singapore [34]</td>
<td>2000</td>
<td>726</td>
<td>30–69</td>
<td>Indians: M: 16.2 μmol/L, F: 11.5 μmol/L, Malays: M: 15.0 μmol/L, F: 12.3 μmol/L, Chinese: M: 15.3 μmol/L, F: 12.2 μmol/L</td>
<td>Total homocysteinaemia &gt;14 μmol/L</td>
<td>Inches: M: 60.0%, F: 21.9%, Malays: M 53.9, F: 37.8%, Chinese: M: 56.6, F: 10.6%</td>
</tr>
<tr>
<td>Canada (Ontario) [107]</td>
<td>2000</td>
<td>711</td>
<td>Mean: 58.4</td>
<td>M: 9.3 μmol/L, F: 8.3 μmol/L</td>
<td>Total homocysteinaemia &gt;15 μmol/L</td>
<td>n. a.</td>
</tr>
<tr>
<td>Australia [108]</td>
<td>1999</td>
<td>365</td>
<td>Mean: 42</td>
<td>M: 14.4 μmol/L, F: 11.9 μmol/L</td>
<td>Total homocysteinaemia &gt;15 μmol/L</td>
<td>24%</td>
</tr>
<tr>
<td>Argentina (Buenos Aires) [109]</td>
<td>2002</td>
<td>196</td>
<td>&gt;65</td>
<td>M: 15.0 μmol/L, F: 12.3 μmol/L</td>
<td>Total homocysteinaemia ≥95th (M: 11.4 μmol/L, F: 10.4 μmol/L)</td>
<td>M: 76.2%, F: 66.4%</td>
</tr>
<tr>
<td>Korea [110]</td>
<td>2002</td>
<td>195</td>
<td>23–72</td>
<td>M: 11.2 μmol/L, F: 9.2 μmol/L</td>
<td>Total homocysteinaemia ≥25 μmol/L</td>
<td>M: 10.1%, F: 2.1%</td>
</tr>
</tbody>
</table>

M: male, F: female n.a.: not available
Homocysteine and CVD: cause, consequence, or merely a marker?

For several reasons, a causal role for homocysteine in the development of CVD is still debated. First, the association between homocysteine and CVD is not marked. A recent meta-analysis of 30 observational studies including 5,073 subjects with IHD and 1,113 with stroke found that a 25% lower homocysteine level was associated with an 11% lower relative risk of IHD and a 19% lower relative risk of stroke. The authors of the study concluded that elevated homocysteine was at most a modest independent predictor of IHD and stroke in healthy populations [9]. Another meta-analysis which included 57 studies found low correlations between homocysteine concentrations and coronary heart and cerebrovascular disease [10].

Secondly, randomised controlled studies have not consistently shown that supplementation with folic acid reduces CVD risk. A randomised controlled trial including high risk CVD patients failed to show a beneficial effect from homocysteine-lowering therapy on CVD markers. Supplementation with folic acid in patients with type 2 diabetes and mild hyperhomocysteinaemia was effective in reducing homocysteine concentrations, but was not associated with any improvement in biochemical markers of endothelial dysfunction or inflammation [75]. Furthermore, homocysteine-lowering therapy in bare-metal stented patients may have moderate benefits at best, or even adverse effects, on restenosis [76, 77]. To our knowledge no similar study has been carried out with drug-eluting stents.

These conflicting findings are in line with studies in individuals with a mutation in the gene coding for MTHFR. If homocysteine was causally linked to CVD, subjects with this gene mutation should be more prone to CVD. Two meta-analyses including 6,000 participants each have been carried out to assess this question [78]. They found no significant (OR: 1.12 [95% CI, 0.92 to 1.37]) [21], or only a weak association (OR: 1.22 [95% CI, 1.01 to 1.47]) [78] between mutations in MTHFR and CVD. Still, these meta-analyses may not have had sufficient statistical power to show an effect of hyperhomocysteinaemia on CVD [7]. However, a recent large meta-analysis including 26,000 cases of CHD and 31,183 controls confirmed the lack of statistically significant association between MTHFR mutations and CHD in subjects living in Europe (OR: 1.08 [95% CI, 0.99 to 1.18]), Asia (OR: 1.23 [95% CI, 0.94 to 1.62]), North America (OR: 0.93 [95% CI, 0.80 to 1.10]) and Australia (OR: 1.04 [95% CI, 0.73 to 1.49]) [25]. In this meta-analysis, the only significant associations were found in the Middle East (OR: 2.61 [95% CI, 1.81 to 3.75]) and Japan (OR: 1.71 [95% CI, 1.23 to 2.37]) [25].

Another meta-analysis including 111 studies showed that among 15,635 healthy subjects (without previous CVD), the mean difference in homocysteine concentration between TT and CC homozygotes was 1.93 μmol/L (95% CI, 1.38–2.47). In a complementary genetic meta-analysis (n = 13,928), the odds ratio for stroke was 1.26 (95% CI, 1.14 to 1.40) for TT versus CC homozygotes, an increased risk consistent with the difference in homocysteine level between polymorphisms [79]. The polymorphism being distributed randomly at the time of gamete formation (Mendelian randomisation [74]), its association with stroke should not be confounded by any other factors (smoking, previous CVD, etc). However, heterogeneity for the effect of the polymorphisms was found: the association was lower in North American studies, which may suggest that gene-environment interactions should be considered [79]. In addition, the size of the effect was small compared with classical CVD risk factors. Finally, studies utilising Mendelian randomisation should be interpreted with caution, as discussed by Nitsch et al. [80].

On another note, recent studies suggest that homocysteine levels may increase secondary to the occurrence of CVD and/or due to the presence of atherosclerosis. For example, subjects with reduced renal function have elevated homocysteine concentrations, which suggests that vascular disease, which may impair renal function, could cause hyperhomocysteinaemia [81, 82]. However, other findings show that hyperhomocysteinaemia is a predictor of CVD in patients with renal failure [83] as well as chronic stable renal transplant recipients [84], independently of renal function. This contradicts the assumption that hyperhomocysteinaemia is caused by renal dysfunction. Hyperhomocysteinaemia may also be secondary to myocardial infarction or stroke [85–90]. In one study, patients had low homocysteine levels during, and briefly after, myocardial infarction or stroke, and had higher homocysteine concentrations later during the convalescent phase [90].

Finally, the association between CVD and homocysteine may result from deficiency of B vitamins per se. In fact, homocysteine may only alter vascular reactivity when folate is simultaneously low. On the other hand, folate is associated with an alteration in vascular reactivity without any change in homocysteine concentrations [91, 92]. In addition, B vitamins were shown to reduce homocysteine without improving endothelial dysfunction or hypercoagulability [93].
More results are needed

To date, no evidence is available which links a reduction in serum homocysteine to a decrease in CVD morbidity or mortality [72, 94]. Results of four large-scale randomised controlled trials are currently available, all of which were carried out in CVD patients (table 3). In one trial, 3,680 stroke patients were randomised to either high or low dose vitamin supplementation. High vitamin supplementation had no significant effect (RR: 1.0 [95% CI, 0.8–1.1]) on vascular outcomes after two years, despite a significant reduction in homocysteine levels of 2 μmol/L [95]. Similar reductions in homocysteine concentrations (2.4 μmol/L) were found in the “HOPE-2” study after treatment with 2.5 mg folic acid, 50 mg vitamin B6 and 1 mg vitamin B12 for five years. In this trial, including 5,522 patients with CVD or diabetes, homocysteine-lowering treatment failed to reduce the risk of major cardiovascular events (RR for death from cardiovascular causes: 0.96 [95% CI, 0.81–1.13], RR for myocardial infarction: 0.98 [95% CI: 0.85–1.14]) [96]. In another trial, 636 patients undergoing bare-metal stenting were randomised to either high doses of B vitamins (1.2 mg folic acid, 48 mg vitamin B6, and 60 μg vitamin B12) for 6 months, or placebo. The administration of high doses of B vitamins lowered homocysteine concentrations significantly, but tended to increase the risk of restenosis (34.5% vs. 26.3%, P = 0.05) [77]. In the “NORVIT” trial 3,749 CVD patients participated. Homocysteine-lowering treatment with folic acid (0.8 mg) plus vitamin B12 (0.4 mg), with or without high doses of vitamin B6 (40 mg) did not lower the risk of recurrent CVD or death after acute myocardial infarction compared with placebo (RR for folic acid plus vitamin B12: 1.08 [95% CI, 0.93–1.25]; RR for folic acid plus vitamin B12 with vitamin B6: 1.22 [95% CI, 1.00–1.50]). The latter association suggests a trend (P = 0.05) towards higher risk in the treated group. Consequently, and in line with the previous study, the authors suggest a harmful effect from a treatment of this kind after acute myocardial infarction [97]. Additional clinical trials are ongoing (table 3). Given the weak association between homocysteine and CVD, sufficient power to detect an effect necessitates the inclusion of a very large number of patients [7]. However, even if these trials show a favourable effect from vitamin supplementation on clinical endpoints, they will not distinguish the effects of vitamin supplementation per se from the effect of lowering homocysteine concentrations. In addition, it may be increasingly difficult to carry out clinical trials on homocysteine, since food fortification with folate has been introduced in several countries such as the United States, Canada [98, 99] and Australia [68]. In these populations, the mean homocysteine concentration has decreased significantly since the introduction of food fortification with folate, and identification of subjects with low folate intake and an associated hyperhomocystinemia may present a challenge [33].

Screening and treatment of hyperhomocysteinaemia

Regular fruit and vegetable intake may have only a moderate impact on elevated homocysteine levels [11, 70, 72, 100, 101]. Hence some authors recommend supplementation with vitamins, e.g. 200–800 μg folate, 3–30 μg vitamin B12, and 2–6 mg vitamin B6 for patients with manifest CVD or high CVD risk (hypertension, dyslipidaemia, diabetes, smoking, family history of premature atherosclerosis), with hyperhomocysteinaemia (>12 μmol/L), and for populations at high risk for vitamin deficiency, in order to target serum homocysteine <10 μmol/L [11–16, 18, 72].

Numerous reports do either not support [9, 10, 25, 94, 102] or discourage [76, 77, 97, 103] these proposals. The current recommendations of major health agencies or other groups regarding screening, prevention and treatment of hyperhomocysteinaemia in the general population or in selected clinical populations are prudent (table 4). None of the agencies recommends homocysteine-reducing vitamin supplementation or screening for hyperhomocysteinaemia. The American Heart Association recently states as part of its diet and lifestyle recommendations [104]: “Available evidence is inadequate to recommend folate and other B vitamin supplements as a means to reduce CVD risk at this time”.

Therefore, we would suggest:

1. No routine determination of homocysteine in the general population.
2. No routine determination of homocysteine in high risk CVD patients.
3. If homocysteine has been measured and found elevated in patients with low CVD risk, no treatment is recommended but increased intake of fruit and vegetables (at least five servings per day) and regular physical activity is recommended. No further blood homocysteine determinations are necessary.
4. For individuals with a high homocysteine level and a high CVD risk:
   a. Ensure control of “classical” CVD risk factors (e.g. tobacco, lipids, blood pressure and diabetes).
<table>
<thead>
<tr>
<th>Study name [reference]</th>
<th>Region</th>
<th>Sample size</th>
<th>Study population</th>
<th>Baseline Homocysteine levels</th>
<th>Studied outcome</th>
<th>Intervention</th>
<th>Main result(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine [SEARCH] [111]</td>
<td>United Kingdom (Oxford)</td>
<td>12,064</td>
<td>Patients with myocardial infarction Population without mandatory folate fortification of food</td>
<td>n.a.</td>
<td>Myocardial infarction</td>
<td>2 × 2 factorial design: folic acid, 2 mg/d, and vitamin B12, 1 mg/d, compared with placebo; simvastatin, 80 mg/d, compared with 20 mg/d</td>
<td>Ongoing study</td>
</tr>
<tr>
<td>Prevention with a Combined Inhibitor and Folate in Coronary Heart Disease [PACIFIC] Study [112]</td>
<td>Australia</td>
<td>10,000</td>
<td>Patients with coronary heart disease Population with voluntary folate fortification of food</td>
<td>10.9 and 11.1 μmol/L</td>
<td>Arterial vascular disease</td>
<td>3 × 3 factorial design: folic acid, 0.2 or 2 mg/d, compared with placebo; angiotensin-converting enzyme inhibitor at 2 doses compared with placebo</td>
<td>Ongoing study</td>
</tr>
<tr>
<td>Vitamins to Prevent Stroke [VITATOPS] Study [113, 114]</td>
<td>Australia</td>
<td>8,000</td>
<td>Patients with stroke or transient ischaemic attack Population with and without mandatory folate fortification of food</td>
<td>12.8 and 13.4 μmol/L</td>
<td>Stroke</td>
<td>Folic acid, 2 mg/d, plus vitamin B6, 25 mg/d, plus vitamin B12, 0.4 mg/d, compared with placebo</td>
<td>Ongoing study</td>
</tr>
<tr>
<td>Heart Outcomes Prevention Evaluation [HOPE-2] Study [96]</td>
<td>Canada</td>
<td>5,522</td>
<td>Patients (age: &gt;55 years) with vascular disease or diabetes Population with and without mandatory folate fortification of food</td>
<td>12.2 μmol/L</td>
<td>Cardiovascular events</td>
<td>Folic acid, 2.5 mg/d; vitamin B6, 50 mg/d; plus vitamin B12, 1 mg/d</td>
<td>No reduction of major cardiovascular events (RR for death from cardiovascular causes: 0.96 [95% CI, 0.81–1.11], RR for myocardial infarction: 0.98 [95% CI, 0.89–1.14])</td>
</tr>
<tr>
<td>Women’s Antioxidant and Cardiovascular Disease Study [WACS] [115]</td>
<td>United States</td>
<td>5,442</td>
<td>Female health professionals (age: &gt;40 years) Population with mandatory folate fortification of food</td>
<td>n.a.</td>
<td>Myocardial infarction, stroke, coronary revascularization and total CVD mortality</td>
<td>Folic acid, 2.5 mg/d, plus vitamin B6, 50 mg/d, plus vitamin B12, 1 mg/d, compared with placebo</td>
<td>Ongoing study</td>
</tr>
<tr>
<td>Folic Acid for Vascular Outcome Reduction In Transplantation (FAVORIT) trial [116]</td>
<td>United States</td>
<td>4,000</td>
<td>Renal transplant recipients Population without mandatory folate fortification of food</td>
<td>17.4 μmol/L</td>
<td>Cardiovascular events</td>
<td>Folic acid, 1.0 or 0 mg/d, vitamin B6, 50 or 1.4 mg/d and vitamin B12, 1 or 0.002 mg/d</td>
<td>Ongoing study</td>
</tr>
<tr>
<td>Norwegian Study of Homocysteine Lowering with B-Vitamins in Myocardial Infarction [NORVIT] [97]</td>
<td>Norway</td>
<td>3,749</td>
<td>Patients with acute myocardial infarction within 7 days before randomisation Population without mandatory folate fortification of food</td>
<td>12.9-13.3 μmol/L</td>
<td>Myocardial infarction</td>
<td>2 × 2 factorial design: folic acid, 0.8 mg/d, vitamin B6, 0.4 mg, vitamin B12, 40 mg/d; folic acid, 0.8 mg/d, vitamin B12, 0.4 mg, vitamin B6, 40 mg/d; placebo</td>
<td>No reduction of the risk of recurrent cardiovascular disease (RR for folic acid plus vitamin B6: 1.08 [95% CI, 0.91–1.25]), Possible harmful effect from combined B vitamin treatment (RR for folic acid plus vitamin B12 with vitamin B6: 1.22 [95% CI, 1.00–1.50])</td>
</tr>
<tr>
<td>Vitamins in Stroke Prevention [VISP] Trial [99]</td>
<td>United States</td>
<td>3,680</td>
<td>Patients with nondisabling cerebral infarction Mainly populations with mandatory folate fortification of food</td>
<td>13.4 μmol/L</td>
<td>Stroke</td>
<td>Folic acid, 2.5 mg/d, vitamin B6, 25 mg/d, and vitamin B12, 0.4 mg/d, compared with folic acid, 0.02 mg/d, plus vitamin B6, 0.2 mg/d, plus vitamin B12, 0.06 mg/d</td>
<td>No effect of homocysteine lowering treatment on vascular outcomes despite moderate reduction of homocysteine concentration (RR: 1.0) [95% CI, 0.8 to 1.1])</td>
</tr>
</tbody>
</table>
### Table 3 cont.

<table>
<thead>
<tr>
<th>Study name [reference]</th>
<th>Region</th>
<th>Sample size</th>
<th>Study population</th>
<th>Baseline Homocysteine levels</th>
<th>Studied outcome</th>
<th>Intervention</th>
<th>Main result(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Norway B-vitamin Intervention Trial (WENBIT) [117]</td>
<td>Norway</td>
<td>3,000</td>
<td>Patients with coronary artery disease Population without mandatory folate fortification of food</td>
<td>11.1 μmol/L</td>
<td>Cardiovascular events</td>
<td>2 × 2 factorial design: folic acid, 0.8 mg/d, vitamin B₁₂, 0.4 mg, vitamin B₆, 40 mg/d, folate acid, 0.8 mg/d, vitamin B₁₂, 0.4 mg, vitamin B₆, 40 mg/d, placebo</td>
<td>Ongoing study</td>
</tr>
<tr>
<td>SU.FOL.OM3 study [118]</td>
<td>France</td>
<td>3,000</td>
<td>Patients with myocardial infarction, unstable angina pectoris or ischaemic stroke Population without mandatory folate fortification of food</td>
<td>n.a.</td>
<td>Recurrent ischaemic diseases</td>
<td>Folate (in the natural 5-methyl-tetrahydrofolate form) in combination with vitamin B₁₂ and B₁, and/or omega-3 fatty acids and/or placebo</td>
<td>Ongoing study</td>
</tr>
<tr>
<td>Homocysteinaemia in kidney and end stage renal disease (HOST) study [119]</td>
<td>United States</td>
<td>2,000</td>
<td>Patients with end stage renal disease or advanced chronic kidney disease Population without mandatory folate fortification of food</td>
<td>n.a.</td>
<td>All cause mortality, myocardial infarction, stroke, amputation of a lower extremity</td>
<td>Folic acid, 40 mg/d, vitamin B₆, 100 mg, vitamin B₁₂, 2 mg compared with placebo</td>
<td>Ongoing study</td>
</tr>
<tr>
<td>Cambridge Heart Antioxidant Study [CHAOS-2] [120]</td>
<td>United Kingdom</td>
<td>1,882</td>
<td>Cardiovascular patients Population without mandatory folate fortification of food</td>
<td>n.a.</td>
<td>Myocardial infarction, unstable angina</td>
<td>Folic acid, 5 mg/d, compared with placebo</td>
<td>Ongoing study</td>
</tr>
<tr>
<td>Folate therapy and in-stent restenosis after coronary stenting [77]</td>
<td>Germany (Bremen) &amp; Netherlands (Zwolle)</td>
<td>636</td>
<td>Bare-metal coronary stented patients Population without mandatory folate fortification of food</td>
<td>12.2 and 12.9 μmol/L</td>
<td>Restenosis</td>
<td>Folic acid, 1 mg, vitamin B₁₂, 5 mg and vitamin B₁₂, 1 mg intravenous bolus, then folic acid, 1.2 mg/d plus vitamin B₁₂, 48 mg/d plus vitamin B₁₂, 0.06 mg/d compared with placebo</td>
<td>Homocysteine lowering treatment may increase the risk of in-stent restenosis (34.5% vs. 26.5% in placebo, P = 0.05) and the need for target-vessel revascularisation (15.8% vs. 10.6% in placebo, P = 0.05)</td>
</tr>
<tr>
<td>Transplant Study [103]</td>
<td>Italy</td>
<td>51</td>
<td>De novo heart transplant recipients (mean age: 53 years) Population without mandatory folate fortification of food</td>
<td>17.9 μmol/L</td>
<td>Coronary allograft vasculopathy (CAV)</td>
<td>Folic acid, 15 mg/d compared with placebo</td>
<td>Despite being effective in preventing hyperhomocysteinaemia after heart transplantation, folate therapy does not affect early CAV onset.</td>
</tr>
</tbody>
</table>

n.a.: not available
b. Recommend increased intake of fruit and vegetables (at least five servings per day) and regular physical activity.

c. No clear evidence for or against oral supplementation with folate, vitamins B<sub>6</sub> and B<sub>12</sub> if “a” and “b” are not achievable.

d. Further blood homocysteine determinations are disputable.

### Conclusion

Homocysteine is associated with a risk of cardiovascular and cerebrovascular diseases and venous thrombosis. However, there are insufficient and inconsistent data from which to draw conclusions as to whether homocysteine is causally linked with these diseases. In addition, there is currently no evidence that homocysteine-lowering therapy has a beneficial effect on CVD risk. The current body of evidence further precludes recommending screening for homocysteine at population level or food-fortification with B vitamins to reduce overall CVD risk. For clinicians, the objective should be to reduce the overall CVD risk in hyperhomocysteinemic individuals by controlling “classical” risk factors such as smoking, elevated blood pressure, adverse lipid profiles and diabetes, and by promoting a healthy lifestyle.

### Search strategy and selection criteria

Publications of interest were randomised controlled trials, animal and in vitro studies, literature reviews, meta-analysis and epidemiological studies (cohort or case-control studies). Publications were identified by systematic searches of MEDLINE 1980–2006 using the following keywords per se and in combination: “homocysteine”, “hyperhomocysteinaemia”, “folic acid”, “vitamins”, “deficiency”, “cardiovascular risk factor”, “cardiovascular disease”, “treatment” and “supplementation”. Although we concentrated on recent findings we also included some older research milestones.

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105 Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew


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