Potential Clinical and Economic Effects of Homocyst(e)ine Lowering

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Background: Elevated total homocyst(e)ine levels (≥11 µmol/L) have been identified as a potential risk factor for coronary heart disease. However, the benefits expected from lowering homocyst(e)ine levels with folic acid and vitamin B₁₂ supplementation have yet to be demonstrated in clinical trials.

Subjects and Methods: We constructed a decision analytic model to estimate the clinical benefits and economic costs of 2 homocyst(e)ine-lowering strategies: (1) “treat all”—no screening, daily supplementation with folic acid (400 µg) and vitamin B₁₂ (cyanocobalamin; 500 µg) for all; (2) “screen and treat”—screening, followed by daily supplementation with folic acid and vitamin B₁₂ for individuals with elevated homocyst(e)ine levels. Simulated cohorts of 40-year-old men and 50-year-old women in the general population were evaluated. In the base-case analysis, we assumed that lowering elevated levels would reduce excess coronary heart disease risk by 40%; however, this assumption and others were evaluated across a broad range of potential values using sensitivity analysis. Primary outcomes were discounted costs per life-year saved.

Results: Although the treat-all strategy was slightly more effective overall, the screen and treat strategy resulted in a much lower cost per life-year saved ($13600 in men and $27500 in women) when compared with no intervention. Incremental cost-effectiveness ratios for the treat-all strategy compared with the screen and treat strategy were more than $500000 per life-year saved in both cohorts. Sensitivity analysis showed that cost-effectiveness ratios for the screen and treat strategy remained less than $50000 per life-year saved under several unfavorable scenarios, such as when effective homocyst(e)ine lowering was assumed to reduce the relative risk of coronary heart disease–related death by only 11% in men or 23% in women.

Conclusions: Homocyst(e)ine lowering with folic acid and vitamin B₁₂ supplementation could result in substantial clinical benefits at reasonable costs. If homocyst(e)ine lowering is considered, a screen and treat strategy is likely to be more cost-effective than universal supplementation.

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SUBJECTS AND METHODS

DECISION ANALYTIC MODEL

We constructed a decision analytic model to estimate the clinical and economic outcomes of 3 strategies: (1) “no intervention”—no screening or treatment for at-risk persons; (2) “treat all”—no screening, a daily supplement with folic acid and vitamin B₁₂ (cyanocobalamin) for all at-risk persons; and (3) “screen and treat”—screening at-risk persons with a single tHcy measurement, followed by a daily supplement with folic acid and vitamin B₁₂ for those with tHcy levels of 11 µmol/L or more (Figure 1).

We assessed each strategy in 2 hypothetical cohorts: 40-year-old men and 50-year-old women. We chose these cohorts because each represents a demographic group from the general population considered “at risk” for developing CHD.¹⁶

Each strategy was evaluated in 2 successive stages. First, with a decision tree using clinical inputs and cost estimates specific to each strategy, we determined (1) the likelihood of identifying elevated tHcy levels (if screening occurred), (2) the effectiveness of folic acid at lowering tHcy levels, and (3) initial costs. Next, Markov simulations incorporating age-, sex-, and CHD-specific mortality rates were generated to estimate the effect of tHcy lowering on survival and ongoing costs. Cycles during the simulation were 1 year, with subjects continued in the model until age 85 years or death. The outcomes we assessed were overall life expectancy in discounted life-years and total costs in discounted 1998 dollars. Both life-years and costs were discounted at an annual rate of 3%.¹⁷

LIKELIHOOD OF CLINICAL EVENTS

Table 1 lists the probabilities and ranges of clinical events used in the decision model. We reviewed the published literature to determine the best estimates for the base-case analysis. For highly uncertain estimates—such as the effectiveness of tHcy lowering on CHD risk reduction—we used conservative values for the base-case analysis and then evaluated the estimate across a broad range of potential values using sensitivity analysis.

DISTRIBUTION, RELATIVE RISK, AND MEASUREMENT OF tHcy LEVELS

To estimate the distribution of tHcy levels in each cohort, we analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III).¹⁸ A population-based survey of noninstitutionalized civilians in the United States. NHANES III contains nationally sampled data from 1991 to 1994 on age- and sex-specific tHcy levels in the general population. Based on these data, 40% of men 40 years or older and 32% of women 50 years or older had tHcy levels at 11 µmol/L or more. However, since recent low-level fortification of US cereal and grain products with folic acid (starting in January 1998) might have lowered tHcy levels in the general population, we varied these prevalence estimates extensively during sensitivity analysis.¹⁹ We used the statistically pooled results of a published meta-analysis to estimate the relative risk of death from CHD at various tHcy levels.⁶ To be conservative, we used the lower bound value from the 95% confidence interval of the pooled odds ratio for our relative risk estimate. Relative risk for CHD-related death was estimated as a gradual dose-related phenomenon: rising by 1.07 for each micromole per liter increase in tHcy from 11 to 15 µmol/L, until maximized at 1.43 for subjects with levels at 15 µmol/L or more.⁸

Using 11 µmol/L as the threshold for initiating treatment, we calculated the sensitivity and specificity of a single tHcy measurement at detecting individuals with elevated levels. To calculate estimates of the test characteristics, we used a known coefficient of variation for the tHcy assay and assumed a normal distribution for tHcy in the cohorts. Test characteristics determined the likelihood that an individual was advised to begin treatment in the screen and treat strategy. Because there is likely to be variability among different laboratories that measure tHcy, we varied sensitivity and specificity estimates across a broad range during sensitivity analysis. Moreover, while a treatment threshold of 11 µmol/L was used for both men and women in the base-case analysis, we assessed the effects of varying this cutoff with sensitivity analysis.

EFFECTIVENESS OF FOLIC ACID AT LOWERING ELEVATED tHcy TO LESS THAN 11 µmol/L

Treatment for the screen and treat and treat-all strategies consisted of a daily supplement containing 400 µg of folic acid and 300 µg of vitamin B₁₂. We chose this specific dose of folic acid since it has been shown to be effective at lowering elevated tHcy levels⁵ and is widely available as an over-the-counter supplement. Vitamin B₁₂ was included

RESULTS

BASE-CASE ANALYSIS

Results from the base-case analysis are shown in Table 2. Both the treat-all and screen and treat strategies lowered CHD mortality rates and increased life expectancy compared with the no intervention group. The treat-all strategy led to slightly greater clinical benefits than the screen and treat strategy, yielding 8.7 vs 8.5 life-years saved per 1000 men and 3.9 vs 3.7 life-years saved per 1000 women. The screen and treat strategy resulted in lower overall costs, however, costing $116 per man screened and $103 per woman screened (compared with $278 per man treated and $302 per woman treated in the treat-all strategy). The cost per life-year saved in the screen and treat strategy was $13600 in men and $27 500 in women; for the treat-all strategy, the corresponding cost-effectiveness ratios were $32 000 and $77 500 per life-year saved in men and women, respectively. In comparison to the screen and treat strategy, the incremental cost-effectiveness ratios for the treat-all strategy were $62 000

Continued on next page
because of the concern that folic acid could mask vitamin B12 deficiency, considered the most important adverse effect of folic acid use.20 Since this concern has never been confirmed,21 we also assessed the use of supplements with folic acid alone in sensitivity analysis.

In the base-case analysis, we conservatively estimated that 50% of individuals would use the supplements regularly enough throughout the simulation to derive benefits from treatment. Lower (25%) and higher (75%) adherence rates were evaluated with sensitivity analysis, using rates from clinical trials of aspirin and lipid-lowering agents in the general population as surrogate estimates.22,23 Noncompliant individuals derived no benefits and incurred no ongoing costs.

The effectiveness of folic acid at lowering tHcy levels is reported as variable, with individual responses to treatment dependent on numerous factors such as nutritional status, genetic conditions, and renal function.3,13 Between 40% and 67% of elevated tHcy levels have been attributed to nutritional deficiencies in folic acid and the B vitamins.20,24 We therefore estimated that elevated tHcy levels would be successfully lowered to less than 11 mmol/L in 50% of those who received and adhered to folic acid and vitamin B12 treatment. Initial responses of tHcy levels to folic acid were assumed to remain unaltered throughout the duration of the simulation (ie, successfully reduced levels remained less than 11 mmol/L, while nonresponders continued to have elevated levels).

EFFECTIVENESS OF tHcy LOWERING AT REDUCING CHD-RELATED DEATH

After screening and/or treatment in the decision tree, CHD mortality and overall life expectancy were estimated using a Markov process.25 Baseline mortality rates were obtained for each cohort from age- and sex-specific life tables26 and then modified based on (1) the relative risk for CHD-related death associated with the initial tHcy levels and (2) the estimated level of CHD risk reduction that occurred with effective tHcy lowering. In the base-case analysis, we estimated that 40% of excess tHcy-associated CHD risk would be eliminated if elevated tHcy levels were lowered to less than 11 mmol/L. Therefore, in individuals with initial tHcy levels at 15 mmol/L or more, lowering levels to less than 11 mmol/L reduced the relative risk of CHD-related death from 1.4 to 1.24, ie, 1.4−(1.4−1)×0.40. Because the true level of CHD risk reduction is highly uncertain, we used sensitivity analysis to fully evaluate this estimate from a worst-case scenario (0% relative risk reduction in tHcy-associated CHD) to a best-case scenario (full or 100% relative risk reduction in tHcy-associated CHD).

COSTS

Both direct (ie, specimen analysis) and indirect (ie, phlebotomy, specimen storage) costs were included in the overall cost estimate for a tHcy assay (University of Michigan Laboratory, 1998). The costs of folic acid supplements with or without vitamin B12 were based on wholesale drug prices.27 The cost per person in each strategy included the cost of the tHcy assay (if screening occurred) and the lifetime costs of daily supplements for those treated. Because we assumed that the 2 intervention strategies occurred during routine health maintenance examinations, we did not include the costs of additional clinical visits in the base-case analysis. The base-case analysis also did not include direct costs from the treatment of fatal CHD events or medical care costs attributable to prolonged survival. However, the impact of including costs from additional clinic visits (S75), medical care costs from the treatment of fatal CHD events (S9757),28 and annual costs attributable to prolonged survival (S2588)29 were evaluated with sensitivity analysis.

COST-EFFECTIVENESS RATIOS AND SENSITIVITY ANALYSES

To compare clinical outcomes and economic costs, we calculated cost-effectiveness ratios (in discounted dollars per discounted life-year saved) for the screen and treat and treat-all strategies using the no intervention strategy as the reference group. Because the treat-all strategy resulted in additional life-years saved at additional costs compared with the screen and treat strategy, we calculated incremental cost-effectiveness ratios between the 2 interventions.

We performed a series of 1-way sensitivity analyses to evaluate the effect of uncertainty on the model’s final outcomes. Since the impact of tHcy lowering on CHD risk remains highly uncertain, our main objective was to determine the necessary level of relative risk reduction in CHD from tHcy lowering for the intervention strategies to result in favorable cost-effectiveness ratios. Although arbitrary, we used a value of 500000 per life-year saved—suggested by Goldman and others25,13—as our threshold for defining “cost-effective” health care interventions. Additional 1-way sensitivity analyses assessed how changes in other model parameters altered cost-effectiveness ratios.

per additional life-year saved in men and $1270000 per additional life-year saved in women.

SENSITIVITY ANALYSES

As the effectiveness of tHcy lowering on CHD risk was varied from no effect (worst case) to full risk reduction (best case), cost-effectiveness ratios for both the screen and treat and treat-all strategies declined. The cost per life-year saved in the screen and treat strategy remained below $50000 when the relative risk of CHD-related death was reduced by at least 11% in men and 23% in women (Figure 2). Higher levels of CHD risk reduction were required in the treat-all strategy—more than 25% in men and 60% in women—for cost-effectiveness ratios to be remain lower than $500000 per life-year saved.

We performed additional 1-way sensitivity analyses to determine if uncertainty in other model parameters substantially influenced the results. In the screen and treat strategy, we assessed a worst-case scenario in which both the sensitivity and specificity of the tHcy assay were at 80%. Under this scenario, cost-effectiveness ratios in the screen and treat strategy were $20000 and $44000 per life-year saved in men and women, respectively. After varying the threshold for treatment from 11 to 15 µmol/L, we found that a tHcy level of 11 µmol/L was the most cost-effective level for initiating supple-
mentation in the screen and treat strategy. For example, the incremental cost per additional life-year saved for the 11-µmol/L threshold compared with the 12-µmol/L threshold was near or below $50000 in both cohorts (men, $26300; women, $51000).

Because the connection between folic acid and the masking of vitamin B₁₂ deficiency is not firmly established, we evaluated the use of folic acid supplements without vitamin B₁₂. If folic acid alone was used, the cost per life-year saved in the screen and treat strategy was reduced to $7300 in men and $15400 in women and in the treat-all strategy to $8700 and $21000, respectively, compared with no intervention. The incremental cost-effectiveness ratios between the 2 intervention strategies were $26300 and $51000 in men and $26300 and $51000 in women, respectively.

Figure 1. Decision tree for the screen and treat strategy for persons with total plasma homocyst(e)ine (tHcy) levels of 11 µmol/L or more. CHD indicates coronary heart disease; M, Markov node.

Table 1. Clinical and Economic Estimates Used in the Decision Analytic Model*

<table>
<thead>
<tr>
<th>Model Parameter</th>
<th>Best Estimate</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population prevalence of tHcy levels, %</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>&lt;11 µmol/L</td>
<td>60.5</td>
<td>68.0</td>
<td>50-80</td>
</tr>
<tr>
<td>11-12 µmol/L</td>
<td>9.4</td>
<td>6.9</td>
<td>4.8-11.9</td>
</tr>
<tr>
<td>12-13 µmol/L</td>
<td>6.4</td>
<td>5.8</td>
<td>3.2-8.1</td>
</tr>
<tr>
<td>13-14 µmol/L</td>
<td>6.4</td>
<td>5.1</td>
<td>3.2-8.1</td>
</tr>
<tr>
<td>14-15 µmol/L</td>
<td>4.2</td>
<td>3.7</td>
<td>2.1-5.3</td>
</tr>
<tr>
<td>≥15 µmol/L</td>
<td>13.1</td>
<td>10.6</td>
<td>6.7-16.6</td>
</tr>
<tr>
<td>Relative CHD risk for tHcy levels</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>&lt;11 µmol/L</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>11-15 µmol/L</td>
<td>1.07 per µmol/L</td>
<td>1.07 per µmol/L</td>
<td>NA</td>
</tr>
<tr>
<td>≥15 µmol/L</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>tHcy assay, %</td>
<td>Men</td>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>97</td>
<td>96</td>
<td>80-99</td>
</tr>
<tr>
<td>Specificity</td>
<td>97</td>
<td>98</td>
<td>80-99</td>
</tr>
<tr>
<td>Adherence rate with folic acid therapy, %</td>
<td>50</td>
<td>50</td>
<td>25-75</td>
</tr>
<tr>
<td>Effectiveness of folic acid at lowering tHcy</td>
<td>50</td>
<td>50</td>
<td>40-67</td>
</tr>
<tr>
<td>to &lt;11 µmol/L, %</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Cost of tHcy assay, $</td>
<td>41</td>
<td>41</td>
<td>22-107</td>
</tr>
<tr>
<td>Annual cost of supplementation, $</td>
<td></td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>With folic acid and B₁₂ (base-case)</td>
<td>16.16</td>
<td>16.16</td>
<td>3-25</td>
</tr>
<tr>
<td>With folic acid</td>
<td>4.38</td>
<td>4.38</td>
<td>3-25</td>
</tr>
<tr>
<td>Reduction in excess tHcy-associated CHD risk after lowering tHcy to &lt;11 µmol/L, %</td>
<td>40</td>
<td>40</td>
<td>0-100</td>
</tr>
</tbody>
</table>

*thcy indicates plasma total homocyst(e)ine levels; CHD, coronary heart disease; and NA, not available.
Cost-effectiveness ratios remained less than $32000 per life-year saved even at extreme values, suggesting that uncertainty in these parameters had only a modest effect on outcomes. Finally, when we included the medical care costs of treating fatal cardiovascular events and the annual medical care costs attributable to prolonged survival in the model, the risk reduction thresholds for cost-effectiveness in the intervention strategies were not affected.

Deciding whether to test for or treat elevated tHcy levels in the general population is controversial. Although several studies have suggested an association between elevated tHcy levels and CHD, no evidence from controlled trials is available to confirm that lowering elevated tHcy levels with folic acid leads to better clinical outcomes. Since ongoing trials—most involving subjects with established CHD—are still several years from completion, several authorities are recommending that all middle-age US adults begin consuming daily folic acid supplements (ie, a treat-all strategy) \[^{10,12}\]. Their logic is that supplements with folic acid are safe and inexpensive, so the likely benefits from this intervention outweigh its potential costs. If folic acid supplements are recommended to the general population, however, an alternative strategy of screening followed by targeted treatment (ie, a screen and treat strategy) should also be considered.

The primary objective of our investigation was to use formal decision analytic techniques to evaluate these 2 potential strategies of folic acid supplementation. Specifically, we wanted to determine which intervention was more likely to be cost-effective based on the best available data. Because the true cardiovascular benefits of tHcy lowering are uncertain, we evaluated both interventions over an entire range of tHcy-associated CHD risk reduction.

Two conclusions can be drawn from our results. First, the screen and treat strategy is the more cost-effective intervention. While the treat-all strategy resulted in slightly more life-years saved, its incremental cost per additional life-year saved remained extremely high even when we assumed worst-case scenarios for the sensitivity, specificity, and cost of the tHcy assay. We did find, however, that the incremental cost-effectiveness ratios between the 2 intervention strategies declined considerably (eg, from $6200000 to $500000 per life-year saved).
saved in men) when folic acid supplements without vitamin B₁₂ were used. Determining whether vitamin B₁₂ should be included in folic acid supplements is therefore an important policy consideration.

Second, we found the cost-effectiveness ratios for the screen and treat strategy to be between $10000 and $30000 per life-year saved in the base-case analyses. These results are comparable to cost-effectiveness ratios for traditional CHD interventions in the general population (Table 4). In addition, the screen and treat strategy remained cost-effective under rather unfavorable scenarios such as when a low level of CHD risk reduction was assumed. For example, when we assumed that effective tHcy lowering reduced the relative risk of death from tHcy-associated CHD by only 11% in men or 23% in women, cost-effectiveness ratios for the screen and treat strategy remained less than $50000 per life-year saved (Figure 2). This last result has important implications. First, clinical trials designed to evaluate the effects of folic acid and tHcy lowering on CHD should be powered to detect these cost-effectiveness differences in risk reduction. More important, the fact that the screen and treat strategy is cost-effective at such modest levels of CHD risk reduction makes it reasonable to consider implementing this intervention now while we wait for conclusive data.

One intervention suggested in the literature, but not evaluated in this study, involves further fortification of the US food supply with folic acid. To prevent neural tube defects, cereal and grain products in the United States have been fortified with folic acid since January 1998 at 140 µg per 100 g of cereal, a level considered only partially effective at lowering tHcy levels. Although suggestions have been made that the current level be increased to further reduce tHcy levels in the general population, the Food and Drug Administration has been cautious and is waiting until more evidence on the impact of the 1998 standard can be obtained and reviewed. It is possible, for instance, that manufacturers are already adding more than 140 µg of folic acid per 100 g of cereal to be certain that they are fulfilling current regulations. We did not consider a strategy of additional fortification in our model since it is doubtful that the standard will be changed in the near future, and we were interested in evaluating strategies that physicians might implement now while clinical trials are ongoing. However, we did evaluate how the 1998 standard might affect our results by varying the prevalence estimates of elevated tHcy levels during sensitivity analysis. We found that even if the new fortification level reduced the prevalence of elevated tHcy levels in the general population by 50%—a generous estimate of its effect—the cost-effectiveness ratio for the screen and treat strategy remained less than $20000 per life-year saved for men.

Uncertainty surrounded important estimates in our model. We used the results of a 1995 meta-analysis to estimate the relative risk of death from CHD at various tHcy levels. Because recent prospective studies have noted an inconsistent association between elevated tHcy levels and CHD risk, with both positive and null outcomes found, we used the lower bound of the 95% confidence interval from the pooled odds ratio for our relative risk estimate. We believed that this value was more conservative and consistent with summarized data from other systematic reviews in the literature. For other areas of uncertainty, including the supplement adherence rate and the effectiveness of folic acid at lowering tHcy levels, we used conservative estimates in the base-case analyses to bias our model against the intervention strategies. Altering these estimates during sensitivity analyses did not substantially affect our overall results. Finally, our model did not include the potential benefits from tHcy lowering on other atherosclerotic conditions such as cerebrovascular and peripheral vascular diseases. By not including these potential benefits, our analysis was again more conservative and biased against the interventions.

Our analysis should be considered in the context of the following limitations. The model design did not account for certain real-life complexities: tHcy interactions with other cardiovascular risk factors, tHcy screening at repeated intervals, the potential effects of tHcy lowering on noncardiovascular diseases, and more aggressive interventions with higher folic acid doses with or without additional B vitamins. It has been suggested, for instance, that the addition of vitamin B₆ to folic acid and vitamin B₁₂ strategies could result in further CHD risk reduction. We chose not to include vitamin B₆ in our strategies for 2 reasons: (1) a recent meta-analysis of 12 randomized trials determined that the addition of vitamin B₆ to folic acid and vitamin B₁₂ strategies had no effect on tHcy levels and (2) the relationship between vitamin B₁₂ deficiency and CHD is now thought to be largely independent of its effect on tHcy. Future research and additional analyses will be needed to address these specific concerns.

Despite these limitations, the broad policy implications of our results need to be considered. In 1998, there were an estimated 10.9 million men between the ages of 40 to 44 years and 8.1 million women between the ages of 50 to 54 years in the United States. Under the base-

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### Table 4. Cost-effectiveness Ratios of CHD Interventions in the General Population

<table>
<thead>
<tr>
<th>CHD Intervention</th>
<th>Cost per Life-Year Saved, $†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin for men aged 45-54 y with no heart disease and cholesterol level ≥7.76 mmol/L (≥300 mg/dL)</td>
<td>38 000</td>
</tr>
<tr>
<td>Lovastatin for women aged 45-54 y with no heart disease and cholesterol level ≥7.76 mmol/L (≥300 mg/dL)</td>
<td>1350 000</td>
</tr>
<tr>
<td>Antihypertensive drugs for patients aged 40 y and DBP 95-104 mm Hg</td>
<td>36 000</td>
</tr>
<tr>
<td>Nicotine gum (vs no gum) and smoking cessation advice for men aged 35-69 y</td>
<td>8500</td>
</tr>
<tr>
<td>Nicotine gum (vs no gum) and smoking cessation advice for women aged 35-69 y</td>
<td>12 500</td>
</tr>
<tr>
<td>Regular leisure time physical activity in men aged 35 y</td>
<td>43 000</td>
</tr>
</tbody>
</table>

*Based on data from Tengs et al. CHD indicates coronary heart disease; DBP, diastolic blood pressure. †A 5% annual discount rate, adjusted to 1998 dollars.
case scenario, using the screen and treat strategy would cost nearly $2.1 billion and lead to an estimated 122,000 years of life saved. Similar estimates for the treat-all strategy are $5.5 billion and 126,000 years of life saved.

In summary, we found that strategies to lower tHcy levels with folic acid could lead to substantial cardiovascular benefits at reasonable costs. Of course, controlled clinical trials in the general population and high-risk patient groups are needed to confirm and quantify this potential benefit. Until such trials are completed, however, decision makers will need to assess alternative strategies using limited data from observational studies and decision analytic models. Based on our model, screening 40-year-old men and 50-year-old women with a single tHcy assay followed by the use of folic acid and vitamin B12 supplements in individuals with tHcy levels at 11 μmol/L or more is more cost-effective than universal supplementation and may be a prudent option until definitive data become available.

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