Cost-effectiveness of Vitamin Therapy to Lower Plasma Homocysteine Levels for the Prevention of Coronary Heart Disease: Effect of Grain Fortification and Beyond

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IN 1969, MCCULLY1 PROPOSED HOMOCYSTEINE AS AN ETIOLOGIC AGENT IN THE PATHOGENESIS OF VASCULAR DISEASE. Over the past decade, at least 10 large prospective cohort studies have published data demonstrating a statistically significant association of basal homocysteine levels with coronary heart disease (CHD) events and death.2-11 Nygard et al11 reported that patients with known CHD had a 1.6- to 2.5-fold increase in mortality per each 5-µmol/L (0.68-mg/L) increase in fasting total homocysteine.

Randomized clinical trials have demonstrated that low-dose B vitamins, particularly folic acid and cyanocobalamin, significantly lower homocysteine levels.12-30 A recent meta-analysis by the Homocysteine Lowering Trialists’ Collaboration30 found that folic acid therapy lowered homocysteine levels (standardized at 12 µmol/L [1.62 mg/L]) by 25% and that the addition of cyanocobalamin therapy lowered levels an additional 7%.

Since January 1998, the US Food and Drug Administration (FDA) has required that all enriched grain products contain 140 µg of folic acid per 100 g, a level considered to decrease homocysteine levels.

OBJECTIVES To examine the potential effect of grain fortification with folic acid on CHD events and to estimate the cost-effectiveness of additional vitamin supplementation (folic acid and cyanocobalamin) for CHD prevention.

Design and Setting Cost-effectiveness analysis using the Coronary Heart Disease Policy Model, a validated, state-transition model of CHD events in adults aged 35 through 84 years. Data from the third National Health and Nutrition Examination Survey (NHANES III) were used to estimate age- and sex-specific differences in homocysteine levels.

INTERVENTION Hypothetical comparison between a diet that includes enriched grain products projected to increase folic acid intake by 100 µg/d with the same diet without folic acid fortification; and a comparison between vitamin therapy that consists of 1 mg of folic acid and 0.5 mg of cyanocobalamin and the diet that includes grains fortified with folic acid.

Main Outcome Measures Incidence of myocardial infarction and death from CHD, quality-adjusted life-years (QALYs) saved, and medical costs.

Results Grain fortification with folic acid was predicted to decrease CHD events by 8% in women and 13% in men, with comparable reductions in CHD mortality. The model projected that, compared with grain fortification alone, treating all patients with known CHD with folic acid and cyanocobalamin over a 10-year period would result in 310000 fewer deaths and lower costs. Over the same 10-year period, providing vitamin supplementation in addition to grain fortification to all men aged 45 years or older without known CHD was projected to save more than 300000 QALYs, to save more than US $2 billion, and to be the preferred strategy. For women without CHD, the preferred vitamin supplementation strategy would be to treat all women older than 55 years, a strategy projected to save more than 140000 QALYs over 10 years.

Conclusions Folic acid and cyanocobalamin supplementation may be cost-effective among many population subgroups and could have a major epidemiologic benefit for primary and secondary prevention of CHD if ongoing clinical trials confirm that homocysteine-lowering therapy decreases CHD event rates.

Context A high homocysteine level has been identified as an independent modifiable risk factor for coronary heart disease (CHD) events and death. Since January 1998, the US Food and Drug Administration has required that all enriched grain products contain 140 µg of folic acid per 100 g, a level considered to decrease homocysteine levels.

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Corresponding Author and Reprints: Jeffrey A. Tice, MD, Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, San Francisco, CA 94143-0320 (e-mail: jttice@medicine.ucsf.edu).
ine levels in the general population have decreased. In this study, we first estimated the epidemiologic impact of grain fortification on CHD events and then calculated the additional costs and benefits of further homocysteine lowering using vitamin supplementation. These projections, despite their logic, should be interpreted in the context of the absence of clinical trial data that proves the efficacy of reducing homocysteine levels to prevent myocardial infarction or CHD death.

**METHODS**

**CHD Policy Model**

The Coronary Heart Disease Policy Model is a validated, state-transition model of CHD events and costs among US residents aged 35 through 84 years. The model was recently updated and calibrated using 1980 and 1986 US Vital Statistics to predict CHD mortality within 2% of the reported age- and sex-specific rates in the 1990 US Vital Statistics. We refined the model using data from the third National Health and Nutrition Examination Survey (NHANES III) to estimate the age- and sex-specific distribution of homocysteine levels in the US population (TABLE 1). Validation analyses confirmed that the model incorporating the homocysteine-level distribution predicts CHD mortality within 2% of the 1990 US Vital Statistics. The overall model consists of 3 integrated submodels: the demographic epidemiologic submodel, the bridge submodel, and the disease history submodel. The disease epidemiologic submodel uses population risk factor distributions to predict new CHD events in people with no known CHD. The distributions of smoking status, diastolic blood pressure, high-density lipoprotein levels, and total serum cholesterol levels were derived from the NHANES II. The 4 risk factor distributions were assumed to be independent, conditional on age range and sex. The number of US residents who entered the model each subsequent year was estimated from projections of the US Bureau of the Census.

## Table 1. Age- and Sex-Specific Homocysteine Levels in the US Population: Estimates of the Effects of Homocysteine-Lowering Therapy

<table>
<thead>
<tr>
<th>Group, Age, y</th>
<th>Homocysteine Level, µmol/L, at NHANES III Survey†</th>
<th>After Grain Fortification‡</th>
<th>After Grain Fortification Plus Daily Supplement†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>10.3</td>
<td>9.52 (7.6)</td>
<td>7.47 (21.5)</td>
</tr>
<tr>
<td>45-54</td>
<td>11.0</td>
<td>9.98 (9.3)</td>
<td>7.67 (23.1)</td>
</tr>
<tr>
<td>55-64</td>
<td>11.8</td>
<td>10.6 (10.2)</td>
<td>7.92 (25.3)</td>
</tr>
<tr>
<td>65-74</td>
<td>12.6</td>
<td>11.1 (11.9)</td>
<td>8.15 (26.6)</td>
</tr>
<tr>
<td>75-84</td>
<td>12.7</td>
<td>11.2 (11.8)</td>
<td>8.18 (27.0)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>8.60</td>
<td>8.31 (3.4)</td>
<td>6.96 (16.2)</td>
</tr>
<tr>
<td>45-54</td>
<td>8.88</td>
<td>8.51 (4.2)</td>
<td>7.05 (17.2)</td>
</tr>
<tr>
<td>55-64</td>
<td>9.83</td>
<td>9.18 (6.6)</td>
<td>7.33 (20.2)</td>
</tr>
<tr>
<td>65-74</td>
<td>10.6</td>
<td>9.73 (8.2)</td>
<td>7.56 (22.3)</td>
</tr>
<tr>
<td>75-84</td>
<td>11.2</td>
<td>10.1 (9.8)</td>
<td>7.74 (23.4)</td>
</tr>
</tbody>
</table>

*Age- and sex-specific mean homocysteine values from the third National Health and Nutrition Examination Survey (NHANES III) were smoothed by linear averaging. To convert homocysteine from µmol/L to mg/L divide by 7.397.
†Estimates of the effect of grain fortification on age- and sex-specific homocysteine levels. These measures assume an average increase in folic acid intake of 100 mg per person-day following the US Food and Drug Administration mandate to fortify every 100 g of grain with 140 µg of folic acid. Estimates of the homocysteine levels after grain fortification were derived from an analysis of covariance model limited to clinical trials of vitamin therapy to lower homocysteine using folic acid doses of 200 µg/d or less (% reduction in homocysteine levels from NHANES III lev-
‡Estimates of the homocysteine levels after vitamin supplementation with 1 mg of folic acid and 0.5 mg of cyanocoba-
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COST-EFFECTIVENESS OF HOMOCYSTEINE-LOWERING THERAPY

Table 2. Assumptions About Homocysteine Reduction and Coronary Heart Disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Estimate (Range for Sensitivity Analyses)</th>
<th>Reference, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in homocysteine levels with vitamin therapy (1 mg folic acid, 0.5 mg cyanocobalamin), %*</td>
<td>33 (26-38)</td>
<td>Homocysteine Lowering Trials’ Collaboration,26 1998</td>
</tr>
<tr>
<td>Relative risk reduction per 5-µmol/L decrease of homocysteine levels, µmol/L, %</td>
<td>29 (9-45)</td>
<td>Wald et al,29 1998, Boushey et al,53 1995</td>
</tr>
<tr>
<td>Annual cost per 1 mg of folic acid plus 0.5 mg of cyanocobalamin, US $</td>
<td>20.29 (10-30)</td>
<td>Drug Topics Red Book,24 1997</td>
</tr>
</tbody>
</table>

*The percentage decrease reported is for a person with a pregrain fortification homocysteine level of 12 µmol/L (1.62 mg/L). The percentage reduction is a function of the pretreatment and posttreatment homocysteine levels, absolute and relative declines.60 The estimated proportional reduction of a blood homocysteine level of 12 µmol/L (1.62 mg/L) of folic acid supplementation was 25%, with the addition of a mean of 0.5-mg cyanocobalamin providing an additional 7% reduction for a 32% total decrease.60 Populations with higher pretreatment homocysteine levels had a greater percentage and absolute reduction in homocysteine levels; those with low pretreatment homocysteine levels had almost no change in homocysteine level with vitamin supplementation (Table 1).

In our model, we assumed 100% compliance with therapy for the primary simulations. For sensitivity analyses of compliance, we assumed that everyone would continue to receive homocysteine screening and prescriptions for vitamin supplementation (thus accruing all costs), but only a reduced percentage would take the supplements and accrue benefit.

Effect of Change in Homocysteine Level on CHD Event Rates. We assumed that the relative risk reduction (RRR) from homocysteine-lowering therapy was equivalent for both primary and secondary prevention. We derived summary odds ratios (ORs) for changes in CHD event rates from homocysteine level modification using a standard random-effects model to combine results from studies of homocysteine and CHD.2,3,5,8,10,11,56-70 The summary OR was 0.63 per 5-µmol/L (0.68-mg/L) decrease in total homocysteine level (95% confidence interval [CI], 0.55-0.71). This did not differ by sex, and there were no data supporting an interaction of the risk relationship with age. For the baseline analysis, we used the conservative bound (0.71 per 5 µmol/L [0.68 mg/L], a 29% RRR) as our primary estimate because cross-sectional studies often overestimate the strength of the risk relationship compared with prospective studies and clinical trials. For sensitivity analyses, we used a range from 0.55 to 0.91 (45% to 9% RRR), based on the upper bound of the 95% CI of the random effects model including only prospective studies in the meta-analysis2,3,5,8,10,11 and the lower bound of the full random effects model (Table 2). We did not model any adverse effects of vitamin supplementation.

Fortification of Cereal Grain With Folic Acid. Based on FDA projections, we assumed that fortified cereal grain would increase the folic acid intake of the average US consumer by 100 µg/d.71 We did not model differential increases in folic acid consumption by age and sex. The effect of increasing folic acid intake by 100 µg on total homocysteine level was estimated with the same analysis of covariance model used for modeling vitamin supplementation above, limited to clinical trials using supplements containing less than 200 µg of folic acid.62,63 Grain fortification was estimated to decrease a basal homocysteine level of 12 µmol/L (1.62 mg/L) to 10.7 µmol/L (1.45 mg/L), an 11% reduction. Sensitivity analyses evaluated a reduction as low as 5%. Our estimates virtually replicated the drop in homocysteine levels in the Framingham cohort: the geometric mean homocysteine level was 10.1 µmol/L (1.37 mg/L) before grain fortification was mandated and declined to 9.4 µmol/L (1.27 mg/L) after fortification.64 Our model predicts...
that the group mean would decrease from 10.1 to 9.37 µmol/L (1.37-1.27 mg/L). These lower homocysteine levels were used as the starting point for all subsequent models of primary and secondary prevention.

Secondary Prevention. Our secondary prevention models assumed that persons with clinically manifest CHD (the population of the disease history submodel) would take a daily supplement containing 1 mg of folic acid and 0.5 mg of cyanocobalamin in addition to cereal grain fortification.

Primary Prevention. Primary prevention was modeled as an incremental strategy to secondary prevention. As CHD would become manifest in those untreated, they were assumed to have started receiving supplements. Two strategies were modeled: treat everyone with no known CHD with a daily supplement containing 1 mg of folic acid and 0.5 mg of cyanocobalamin or measure everyone’s homocysteine level and treat only those with a homocysteine level greater than 10 µmol/L (>1.35 mg/L). These strategies were evaluated separately for men and women. For each sex, 5 different age cutoffs were modeled beginning with individuals aged 75 years or older. Younger people were added in 10-year increments. The strategies for each sex were then compared. We assumed that everyone would have had an increased folic acid intake at baseline due to grain fortification.

Time Frame. Both primary and secondary prevention strategies were modeled to begin in the year 2001 and were run through 2010. Flour fortification with folic acid was assumed to have begun on January 1, 1998. Our projections assumed that treatment with vitamin therapy, including flour fortification, had a 2-year delay before affecting CHD event rates, analogous to clinical data used to model cholesterol-lowering therapy in prior studies. This approach biases the model against effectiveness in the youngest individuals because they would miss quality-adjusted life-years (QALYs) that they would accrue due to the intervention well after the year 2010.

Cost Considerations. The cost of the vitamin therapy was estimated to be $20.29 per year based on the median 1997 Red Book average wholesale price of 1 mg folic acid supplements plus the median value of 0.5 mg cyanocobalamin supplements. A range from $10 to $30 was used for sensitivity analyses. We did not assume any extra costs for office visits to implement vitamin therapy since this expense was treated as a routine part of health care maintenance requiring less than 1 minute of time. The cost of the homocysteine assay ($26.32) reflected the 1997 Health Care Financing Administration reimbursement for an amino acid assay (CPT-4 code 8213190) and blood specimen handling.

All costs were converted to 1997 dollars using the Medical Care Component of the Consumer Price Index. The cost effectiveness (CE) ratio was expressed in 1997 dollars per QALY. A 3% discounting rate for costs and benefits was used for the primary projections. The discounting rate was varied from 0% to 5% in sensitivity analyses (Table 2). Costs were calculated using a health care perspective. Patient-time costs, lost productivity, and other non–health care costs were not considered in these models, but the costs of CHD events, hospitalizations, revascularization procedures, and outpatient therapy were included. Before calculating CE ratios, we eliminated strategies that were less effective and either more expensive (dominated) or have a higher incremental CE ratio (fail by extended dominance).

RESULTS

Cereal Grain Fortification With Folic Acid

Using baseline estimates, the model predicted that flour fortification would lead to a 13% reduction in myocardial infarctions in men and an 8% reduction in women with comparable reductions in CHD mortality (Table 3). Using our most conservative assumptions, the estimated reductions in annual CHD mortality rates were 1% to 3%.

Secondary Prevention: Folic Acid and Cyanocobalamin Supplementation Plus Grain Fortification

If, in addition to grain fortification, all patients with known CHD were treated with 1 mg of folic acid and 0.5 mg of cyanocobalamin as supplements to lower their homocysteine levels, it was projected that approximately 310000 fewer CHD deaths would occur over a 10-year period compared with grain fortification alone (Table 4). The estimated absolute reduction in deaths would be greatest in the older age groups in whom mortality from CHD and initial homocysteine levels tend to be higher. Because the baseline homocysteine levels at all ages are higher in men and because age-specific CHD mortality is also higher in men, they were expected to benefit more than women. Treating everyone with known CHD with a vitamin supplement was predicted to save money as well as lives in all age and sex subgroups.
Primary Prevention: Folic Acid and Cyanocobalamin Supplementation Plus Grain Fortification

In men, the model predicted that each of the 10 primary prevention strategies would save lives and money compared with men who would consume fortified grain alone (Figure). Screening men aged 45 years or older with no known CHD and treating those whose homocysteine levels were higher than 10 µmol/L (1.35 mg/L) was predicted to maximize cost savings. Providing vitamin supplementation beyond grain fortification to all men aged 45 years or older was projected to cost $9000/QALY saved compared with screening for elevated homocysteine levels (screen and treat). Extending supplementation to men aged 35 through 44 years had an incremental CE ratio of nearly $100000/QALY and, thus, generally would not be recommended.

In women aged 75 years or older without CHD, vitamin supplementation was predicted to have an incremental CE ratio of $1200/QALY vs grain fortification alone. Screening women aged 65 through 74 years and treating those with elevated homocysteine levels had an incremental CE ratio of $5500/QALY vs treating all women aged 75 years or older. Extending treatment to all women aged 65 years or older was predicted to have an incremental CE ratio of $8800/QALY vs the screen-and-treat strategy. Treating all women aged 55 through 64 years had an incremental CE ratio of $39000/QALY, which is in the range of other commonly recommended therapies. Routine treatment of all women aged 45 years or older ($180000/QALY) or all women aged 35 years or older ($830000/QALY) would be too expensive for routine recommendation.

Primary Prevention With Folic Acid and Cyanocobalamin Supplementation: Sensitivity Analyses

If the RRR of vitamin supplementation is 9% rather than 29%, the primary prevention strategies of treating everyone without measuring homocysteine levels would remain attractive at less than $40000/QALY saved for men aged 55 years or older and women aged 75 years or older. A 2-way sensitivity analysis as-

Table 4. Secondary Prevention: Incremental Benefit Over 10 Years of Folic Acid and Cyanocobalamin Supplementation in US Adults With Coronary Heart Disease (CHD)*

<table>
<thead>
<tr>
<th>Group, Age, y</th>
<th>No. of Myocardial Infarctions Prevented</th>
<th>No. of CHD Deaths Averted</th>
<th>Savings, US $ Millions†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men 75-84</td>
<td>41 000</td>
<td>62 000</td>
<td>1600</td>
</tr>
<tr>
<td>Men 65-74</td>
<td>66 000</td>
<td>74 000</td>
<td>5300</td>
</tr>
<tr>
<td>Men 55-64</td>
<td>57 000</td>
<td>50 000</td>
<td>6400</td>
</tr>
<tr>
<td>Men 45-54</td>
<td>27 000</td>
<td>21 000</td>
<td>4400</td>
</tr>
<tr>
<td>Men 35-44</td>
<td>5600</td>
<td>4300</td>
<td>1100</td>
</tr>
<tr>
<td>Total</td>
<td>196 600</td>
<td>211 300</td>
<td>18 800</td>
</tr>
<tr>
<td>Women 75-84</td>
<td>28 000</td>
<td>48 000</td>
<td>1000</td>
</tr>
<tr>
<td>Women 65-74</td>
<td>25 000</td>
<td>33 000</td>
<td>1800</td>
</tr>
<tr>
<td>Women 55-64</td>
<td>14 000</td>
<td>15 000</td>
<td>1700</td>
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<tr>
<td>Women 45-54</td>
<td>5300</td>
<td>4700</td>
<td>780</td>
</tr>
<tr>
<td>Women 35-44</td>
<td>1100</td>
<td>840</td>
<td>140</td>
</tr>
<tr>
<td>Total</td>
<td>73 400</td>
<td>101 540</td>
<td>5420</td>
</tr>
</tbody>
</table>

* Vitamin supplementation was compared with folic acid grain fortification alone for those aged 75 through 84 years; extending supplementation to each younger 10-year age group was compared with supplementation in the older group.
† Costs are the expense of treatment with vitamin supplements minus the savings from CHD events prevented.

Figure. Incremental Cost-effectiveness of Primary Prevention With Folic Acid and Cyanocobalamin Supplementation

The strategies along the solid line dominate the other strategies. The slope of each line segment represents the incremental cost-effectiveness ratio between 2 prevention strategies. The arrow points to the strategy with the greatest quality-adjusted life-years (QALYs) and a cost-effectiveness ratio below that conventionally considered cost-effective (<$40000/QALY).

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summing less effective lowering of homocysteine values by vitamin therapy (26%) and the weaker association between homocysteine and CHD risk (RRR 9%) demonstrated that the screen-and-treat strategy would cost $29,000/QALY saved for men aged 45 years or older and $42,000/QALY saved for women aged 65 years or older. If the cost of the vitamin supplement decreased to $10 per year in the prior analysis, the screen-and-treat strategy would save costs and lives in men aged 45 years or older and would cost less than $10,000/QALY gained for women aged 65 years or older. If compliance with vitamin supplementation is only 50%, the treat-all strategy’s incremental CE ratios remain less than $50,000/QALY gained for men aged 45 years or older and women aged 65 years or older.

COMMENT
The primary parameter that determines the benefit of homocysteine-lowering therapy for any person or group is their absolute risk of having a CHD event. Age is the single strongest predictor of CHD risk and is readily available to clinicians when making decisions about whether to screen for hyperhomocysteinemia or recommend vitamin supplementation for CHD prevention. Furthermore, homocysteine increases with age in both men and women. At any given age, both CHD risk and homocysteine levels are lower in women, so sex differences were also considered.

There is always uncertainty in the assumptions used to project cost and effectiveness. We performed a systematic literature review to find the best available data. The risk estimates were based on multivariate analyses of data from the Framingham Heart Study, a source of data demonstrated to be accurate. The model’s simplifying use of categories to summarize risk factors has been shown to be comparable to what would be obtained by considering each risk factor on a continuous scale. Furthermore, future projections based on the Coronary Heart Disease Policy Model have been proven consistently accurate in comparison with subsequent prospective trials. For example, the model’s analyses of the cost-effectiveness of cholesterol reduction in patients after experiencing myocardial infarction are similar to those calculated from the results of randomized trials. The Coronary Heart Disease Policy Model also carries the limitation of any state-transition model—the so-called Markov assumption or limited memory for previous states. This problem has been addressed primarily by creating states in the model to account for prior events (myocardial infarction, cardiac arrest, or coronary artery bypass graft surgery) that influence subsequent CHD event rates. Prior analyses using the model suggest that this is not a significant problem.

The major limitation of our projections is the absence of clinical trial data on the effect of homocysteine-lowering therapy on disease rates. Data from a cohort of patients with homocystinuria treated with vitamin therapy provide evidence for biological plausibility. Compared with historical controls, up to a 90% reduction in catastrophic cardiovascular events has been reported. Our conservative baseline estimate of the association between change in homocysteine level and risk of CHD events was equivalent to the lower bound of the 95% CI in the meta-analysis by Boushey et al. It was also more conservative (closer to an OR of 1) than the summary odds ratio in a recent meta-analysis of prospective observational trials. Sensitivity analyses assuming one fourth the effect size of the baseline estimates projected an attractive CE ratio for men aged 55 years or older and women aged 75 years or older.

We decided not to model benefits for diseases other than CHD despite evidence that elevated homocysteine levels are associated with increased risk for stroke and peripheral vascular disease. Therapy with folic acid and cyanocobalamin may also decrease the incidence of pernicious anemia, dementia, and other clinical manifestations of deficiency of these vitamins. We also did not model any negative consequences of vitamin supplementation. Both folic acid and cyanocobalamin are water-soluble vitamins with very low potential for adverse effects. One concern frequently raised when considering population-based folic acid therapy is the potential to accelerate the neurologic sequelae of vitamin B12 deficiency. However, a recent clinical trial demonstrated that oral cyanocobalamin was as effective as parenteral cyanocobalamin in treating multiple etiologies of cyanocobalamin deficiency.

The observational evidence supporting high homocysteine levels as a risk factor for CHD events is strong. Furthermore, clinical trial data demonstrate that homocysteine levels can be lowered by inexpensive and safe doses of folic acid and cyanocobalamin. Nevertheless, recent clinical trials of beta carotene, vitamin E, and hormone replacement therapy have contradicted strong evidence for benefit demonstrated in multiple prospective observational studies. Ultimately, we would recommend homocysteine-lowering therapy routinely only if ongoing clinical trials demonstrate that vitamin therapy reduces clinically important CHD events. In the meantime, since combined therapy with folic acid and cyanocobalamin is well tolerated, it is reasonable to consider routine therapy in men older than 45 years and women older than 55 years.
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REFERENCES
41. 1998Cost-Efffectiveness of Homocysteine-Lowering Therapy

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