Efficacy of Homocysteine-Lowering Therapy With Folic Acid in Stroke Prevention

A Meta-Analysis

Meng Lee, MD; Keun-Sik Hong, MD, PhD; Shen-Chih Chang, PhD; Jeffrey L. Saver, MD

Background and Purpose—Although a lower serum homocysteine concentration is associated with a reduced risk of stroke in epidemiologic studies, randomized, controlled trials have yielded mixed findings regarding the effect of therapeutic homocysteine lowering on stroke prevention. We performed a meta-analysis of randomized, controlled trials to assess the efficacy of folic acid supplementation in the prevention of stroke.

Methods—Salient trials were identified by formal literature search. Relative risk (RR) with 95% CI was used as a measure of the association between folic acid supplementation and risk of stroke, after pooling data across trials in a fixed-effects model.

Results—The search identified 13 randomized, controlled trials that had enrolled 39,005 participants for folic acid therapy to reduce homocysteine in which stroke was reported as an outcome measure. Across all trials, folic acid supplementation was associated with a trend toward mild benefit that did not reach statistical significance in reducing the risk of stroke (RR = 0.93; 95% CI, 0.85–1.03; P = 0.16). The RR for nonsecondary prevention trials was 0.89 (95% CI, 0.79–0.99; P = 0.03). In stratified analyses, a greater beneficial effect was seen in the trials testing combination therapy of folic acid plus vitamins B6 and B12 (RR = 0.83; 95% CI, 0.71–0.97; P = 0.02) and in the trials that disproportionately enrolled male patients (men:women >2; RR = 0.84; 95% CI, 0.74–0.94; P = 0.003).

Conclusions—Folic acid supplementation did not demonstrate a major effect in averting stroke. However, potential mild benefits in primary stroke prevention, especially when folate is combined with B vitamins and in male patients, merit further investigation. (Stroke. 2010;41:1205-1212.)

Key Words: homocysteine • folic acid • stroke • prevention • meta-analysis

Severe hyperhomocysteinemia, a feature of inborn errors of methionine metabolism, is associated with atherosclerosis.1 In experimental studies, homocysteine causes oxidative stress, enhances inflammatory processes, and damages the vascular endothelium.2,3 In epidemiologic studies, elevated homocysteine is linked to ischemic heart disease and stroke.4–6 A meta-analysis of prospective observational studies showed that a 25% lower homocysteine level was associated with an 11% lower ischemic heart disease risk and a 19% lower stroke risk.7 Folate and vitamin B12 are important regulators in homocysteine metabolism, and studies have shown an inverse relation between folate intake and homocysteine level.8,9 Folic acid supplementation has also been associated with a reduction in carotid atherosclerosis progression.10,11 These observations suggest that folic acid supplementation holds promise as a potential therapy for stroke prevention.

Multiple clinical trials have now been performed investigating folic acid for the prevention of cardiovascular and cerebrovascular outcomes in both primary and secondary prevention populations. At least 2 prior meta-analyses have pooled results of trials and reached contrasting conclusions, with 1 suggesting no benefit on cardiovascular end points and another indicating mild benefit in reducing stroke risk.12,13 Also, these systematic reviews did not analyze effects of sex, even though some cohort studies found that higher folate intake was associated with reduced ischemic stroke risk in men but not in women.14–16 Several large trials have been published in the interval since the most recent meta-analysis and offer more evidence on these issues.17–19 We therefore undertook an updated meta-analysis.

Materials and Methods

The study was performed in accordance with the recommendations of the Quality of Reporting of Meta-analysis consensus group.20

Search Strategy

We searched MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials, and the clinical trial registry maintained at clinicaltrials.gov with the terms “homocysteine,” “folate,” “folic acid,” and “cardiovascular.” A funnel plot of the pooled effect size using Forest Plot Maker software indicated no evidence of publication bias.

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acid," “vitamin B12,” “cobalamin,” “vitamin B6,” “pyridoxine,” and “multivitamin” crossed with the terms “cardiovascular disease,” “myocardial infarct,” “myocardial ischemia,” “coronary heart disease,” “angina,” “heart attack,” “stroke,” “cerebrovascular disease,” “cerebrovascular attack,” “brain attack,” “brain infarct,” “brain hemorrhage,” and “intracranial hemorrhage.” We restricted our search to human beings and clinical trials from January 1966 to May 2009. There were no language restrictions. We used the same search strategy to search abstracts in all American Heart Association–sponsored meetings from January 2003 to February 2009 with the American Heart Association Abstract Archive tool (http://www.abstractsonline.com/arch/home.aspx?lookupkey=12345). We also reviewed the Introduction and Discussion sections of retrieved trials and of prior meta-analyses to identify additional trials.

Criteria for inclusion of a study were as follows: (1) the study design was a randomized, controlled trial (RCT); (2) the study included a comparison of folic acid supplementation (with or without vitamins B6 and B12) with inactive or very-low-dose control; (3) the intervention duration was at least 6 months; and (4) total participants and the number of stroke events were reported separately for active treatment and control groups. Participants of any age or of either sex were included. Studies were excluded when the control group received another active therapy that the active treatment group did not receive or when the active treatment group received another therapy in addition to folic acid and B vitamin that the control group did not receive. All data from eligible trials were abstracted in duplicate by 2 investigators independently (M.L. and K.S.H.) with a standard protocol. Discrepancies were resolved by discussion with a third investigator (J.L.S.) and by referencing the original report.

**Statistical Analysis**

Data were analyzed according to the intention-to-treat principle. The Cochrane Collaboration’s Review Manager software package (RevMan 5) was used for the meta-analysis, and R software was used for the meta-regression. Relative risk (RR) with 95% CI was used as a measure of the association between folic acid supplementation and risk of stroke. Heterogeneity was assessed by the probability value of $\chi^2$ statistics and I$^2$, which describes the percentage of variability in the effect estimates that is due to heterogeneity rather than chance.21,22 Heterogeneity was considered significant when the probability value of $\chi^2$ statistics was <0.05. We regarded an I$^2$ of <40% as minimal, 40% to 74% as modest, and >74% as considerable.23 We planned to pool data across trials according to the fixed-effects model based on Mantel-Haenszel methods if considerable heterogeneity, $P<0.05$, or I$^2 \geq 75\%$ was not present.24,25 We also compared results obtained from a fixed-effects model with a random-effects model to address concerns about the influence of small-study effects on the results of a meta-analysis in which there is evidence of between-study heterogeneity.21 Publication bias was estimated visually by funnel plots displaying standard error as the measure of sample size and RR as the measure of treatment effect.26 We also performed a sensitivity analysis to further explore the robustness of our results. To identify any study that might have exerted a disproportionate influence on the summery treatment effect, we removed each individual trial from the meta-analysis 1 at a time. For all analyses, $P<0.05$ was considered statistically significant.

**Results**

The literature review identified 21 articles for detailed assessment, among which 7 were excluded for lack of data on stroke11,27–32 and 1 because it was derived from the same study population as another report (Figure 1).33 Our final analysis included 13 RCTs that had enrolled 39 005 individuals.17–19,34–43 The study design characteristics are presented in Table 1, and the baseline characteristics of the study participants and their homocysteine change at the end of the trial are presented in Table 2. Of the 13 RCTs, 8 reported adequate generation of the allocation sequence and adequate allocation concealment,17–19,34–36 whereas 10 reported adequate blinding of participants and outcome assessors.17–19,34–43 Seven RCTs were done in regions without folic acid fortification,18,34–36,39,41,43 3 in regions with folic acid fortification,17,19,38 and 3 in both fortified and nonfortified regions (ie, partly fortified).37,40,42 All 13 trials included individuals with preexisting conditions: stroke (1 trial),37 coronary heart disease (5 trials),18,35,36,39,43 manifest cardiovascular disease or multiple risk factors for atherosclerosis (2 trials),17,40 end-stage renal disease or advanced chronic kidney disease (4 trials),19,38,41,42

![Figure 1. Flow chart of study selection process.](http://stroke.ahajournals.org/content/early/2010/05/13/STROKEAHA.109.185259.full-fig1.png)
and esophageal dysplasia (1 trial).34 Cerebrovascular events analyzed were combined nonfatal and fatal strokes in 10 trials; for 1 trial each, data were available only on fatal stroke; nonfatal and fatal ischemic stroke; and the composite of nonfatal and fatal stroke plus transient ischemic attack. Neuroimaging was explicitly mentioned as part of the stroke event ascertainment process in 7 trials.17–19,37,39–41

After all 13 RCTs were pooled, the effect of folic acid supplementation (with or without vitamins B6 and B12) on the occurrence of stroke was RR = 0.93, 95% CI, 0.85 to 1.03; P = 0.16 (Figure 2). The total events were 784 among 20 415 participants (3.8%) in the active treatment group and 791 among 18 590 participants (4.3%) in the control group. There was no substantial asymmetrical appearance on the funnel plot (Supplemental Figure I, available online at http://stroke.ahajournals.org). The estimate from a random-effects model (RR = 0.92; 95% CI, 0.82 to 1.03; P = 0.16) was similar to the estimate from a fixed-effects model.

Figure 3 shows the pooled RR for stroke, stratified by stroke subtype, history of stroke, folic acid fortification, homocysteine reduction rate, duration of active treatment, daily dose of folic acid, treatment regimen, preexisting conditions, and sex. The RR for nonsecondary-prevention trials was 0.89 (95% CI, 0.79 to 0.99; P = 0.03). The RR for trials of folic acid plus vitamins B12 and B6 was 0.83 (95% CI, 0.71 to 0.97; P = 0.02), whereas trials of folic acid alone or folic acid plus vitamin B12 did not show any RR change. The RR for male-predominant trials was 0.84 (95% CI, 0.74 to 0.94; P = 0.003), but female-predominant trials did not show a substantial RR change. Male-predominant trials also differed from female-predominant trials in having higher baseline homocysteine concentrations (13.8 vs 12.3 μmol/L), greater reductions in homocysteine levels in the active treatment arm (27.5% vs 18.5%), and higher stroke event rates in control arms (4.3% vs 2.3%).

Reductions in stroke events were also found in the subgroup of trials with substantial achieved homocysteine reductions (>20%), RR = 0.87; 95% CI, 0.77 to 0.98; P = 0.02; and in trials with longer treatment duration (>3 years), RR = 0.87; 95% CI, 0.78 to 0.98; P = 0.02. However, meta-regression did
not demonstrate a substantial linear relation between degree of homocysteine reduction and stroke rate ($P \approx 0.73$) or between length of treatment duration and stroke rate ($P \approx 0.77$; Figure 4).

**Discussion**

Our meta-analysis including 13 RCTs with >39 000 participants found a trend toward mild benefit of folic acid supplementation on the risk of stroke among persons at high cardiovascular risk but did not reach statistical significance. This result contrasts with the prior meta-analysis conducted in 2007,13 which showed a positive result for stroke reduction. The main difference is the inclusion in our analysis of 4 large trials, encompassing 21 881 participants, that have been completed since 2007, which generally found neutral effects.

Several subgroup analyses suggested potential benefit in particular settings, but this must be regarded as hypothesis generating, given the multiplicity of analyses performed. Multiple analyses suggested that trials with treatment regimens of greater intensity or duration were of modest benefit, including trials in which active treatment consisted of vitamins B6 and B12 in addition to folic acid, trials with substantial reductions in homocysteine levels in the active arm, and trials with longer treatment duration. However, meta-regression analyses were discordant, failing to show a linear relation between homocysteine lowering or treatment duration and stroke prevention.

### Table 2. Demographics and Homocysteine (Hcy) at Baseline and Changes

<table>
<thead>
<tr>
<th>Preexisting Condition</th>
<th>No. of Patients</th>
<th>Age, y</th>
<th>Men, %</th>
<th>Previous Stroke, %</th>
<th>Diabetes Mellitus, %</th>
<th>Baseline Hcy, $\mu$mol/L</th>
<th>Hcy Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark et al(^{34})</td>
<td>Esophageal dysplasia</td>
<td>3318</td>
<td>54</td>
<td>44</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Liem et al(^{35})</td>
<td>Acute MI</td>
<td>283</td>
<td>59</td>
<td>70</td>
<td>NR</td>
<td>24</td>
<td>NR</td>
</tr>
<tr>
<td>Toole et al(^{37})</td>
<td>Ischemic stroke</td>
<td>3880</td>
<td>66.3±10.8</td>
<td>63</td>
<td>100</td>
<td>29</td>
<td>13.4</td>
</tr>
<tr>
<td>Wrone et al(^{38})</td>
<td>ESRD</td>
<td>510</td>
<td>60.2±15.1</td>
<td>50</td>
<td>NR</td>
<td>45</td>
<td>33.0±20.4</td>
</tr>
<tr>
<td>Liem et al(^{40})</td>
<td>CHD</td>
<td>593</td>
<td>65.2±9.8</td>
<td>78</td>
<td>7</td>
<td>9</td>
<td>12.1±4.3</td>
</tr>
<tr>
<td>Bonaa et al(^{19})</td>
<td>Acute MI</td>
<td>2815</td>
<td>63.2±11.6</td>
<td>74</td>
<td>4</td>
<td>10</td>
<td>13.1±4.8</td>
</tr>
<tr>
<td>Lonn et al(^{40})</td>
<td>Vascular disease or multiple risk factors for atherosclerosis</td>
<td>5522</td>
<td>68.9±6.9</td>
<td>71</td>
<td>9</td>
<td>40</td>
<td>12.2±1.6</td>
</tr>
<tr>
<td>Righetti et al(^{41})</td>
<td>ESRD</td>
<td>88</td>
<td>64.5±1.8</td>
<td>56</td>
<td>NR</td>
<td>19</td>
<td>34.9±1.4</td>
</tr>
<tr>
<td>Zoungas et al(^{42})</td>
<td>ESRD</td>
<td>315</td>
<td>56±13</td>
<td>68</td>
<td>9</td>
<td>23</td>
<td>27±13</td>
</tr>
<tr>
<td>Jamison et al(^{19})</td>
<td>ESRD and ACKD</td>
<td>2056</td>
<td>65.8±11.7</td>
<td>98</td>
<td>15</td>
<td>55</td>
<td>22.4(18.7–27.3)</td>
</tr>
<tr>
<td>Albert et al(^{17})</td>
<td>CVD or multiple risk factors for atherosclerosis</td>
<td>5442</td>
<td>62.8±8.8</td>
<td>0</td>
<td>NR</td>
<td>21</td>
<td>12.3(9.6–15.5)</td>
</tr>
<tr>
<td>Ebbing et al(^{18})</td>
<td>CHD and/or aortic valve stenosis</td>
<td>2319</td>
<td>61.7±10.1</td>
<td>79</td>
<td>6</td>
<td>12</td>
<td>10.8±4.5</td>
</tr>
<tr>
<td>Collins and Armitage(^{19})</td>
<td>MI</td>
<td>12 064</td>
<td>64±9</td>
<td>83</td>
<td>7</td>
<td>11</td>
<td>13.5±5</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; ESRD, end-stage renal disease; CHD, coronary heart disease; ACKD, advanced chronic kidney disease; CVD, cardiovascular disease; and NR, not reported. Plus-minus values are SD. Values in parentheses are range.

Figure 2. RR (risk ratio) with 95% CI estimates for stroke (active treatment vs control), by trial and pooled. M-H indicates Mantel-Haenszel methods.
We also found that active treatment showed clinical benefit in trials in which men predominated among enrolled patients. This result is concordant with observational studies that showed that higher folate intake is associated with reduced ischemic stroke risk in male US health professionals and male Finnish smokers\textsuperscript{15,16} but not in female US nurses.\textsuperscript{14} Potential explanations for this sex difference are that men have higher stroke event rates, thus increasing study power to detect treatment effects, and that there are sex differences in the severity and treatment responsiveness of hyperhomocysteinemia, both greater in men than in women.

A mild benefit of folic acid supplementation was shown in trials in which stroke was not a qualifying event but not in secondary prevention trials. This observation raises the possibility that homocysteine lowering is beneficial at early stages of vascular disease elaboration but is less effective in the face of established, advanced disease. In a study with participants without diabetes or cardiovascular disease, B

![Figure 3](http://stroke.ahajournals.org/Downloadedfrom)

Figure 3. Effect of folic acid supplementation on the risk of stroke in prespecified subgroups. Hcy indicates homocysteine; FA, folic acid; Vit, vitamin; ESRD, end-stage renal disease; ACKD, advanced chronic kidney disease; and M-H, Mantel-Haenszel methods.
vitamin supplementation significantly reduced the progression of early-stage subclinical atherosclerosis (carotid artery intima/media thickness) but had no effect on the progression of aortic or coronary artery calcification, markers of late-stage atherosclerosis.11

One explanation that has been advanced for neutral results in individual trials of folate therapy is that the spread of fortification of the food supply with folic acid increased the background dietary intake of folate among all enrolled patients, thus diminishing the potential for the active treatment arm to exert a treatment effect. A physiologic study found that low-dose (0.4 mg/d) folic acid treatment, comparable to daily intake and dietary fortification, improved vascular endothelial function but that high-dose (5 mg/d) folic acid treatment provided no additional benefit.44 Whereas plasma 5-methyltetrahydrofolate levels increased proportionately with treatment dose of folic acid, vascular tissue 5-methyltetrahydrofolate showed no further increment with high-dose compared with low-dose folic acid.44 These findings may partly explain the improvement in stroke mortality after folic acid fortification in Canada and the United States.45

Our meta-analysis found a trend toward treatment benefit in trials conducted only or partly in countries without background fortification of the food supply but no evidence of benefit of pharmacologic folate therapy in trials performed wholly in countries with such fortification.

Figure 4. RR of stroke. A, RR of stroke in relation to percentage change in homocysteine concentrations (Mark et al34 and Liem et al35 were excluded because no homocysteine concentrations recorded). B, RR of stroke in relation to active treatment duration (an outlier, Liem et al,26 was excluded).
Some studies reported that homocysteine reduces the concentration of HDL cholesterol in plasma by inhibiting the hepatic synthesis of apolipoprotein A1, the main HDL apolipoprotein.46-47 These studies not only explain the documented inverse correlation between plasma concentrations of HDL cholesterol and homocysteine48 but also raise the real possibility that a homocysteine-induced inhibition of apolipoprotein A1 synthesis is the mechanism linking homocysteine to the development of atherosclerosis. A low concentration of HDL cholesterol has been shown in epidemiologic studies to be predictive of stroke,49 and treatment that increases the level of HDL cholesterol in plasma may be related to regression of atherosclerosis.50 Because most participants in our meta-analysis were persons at high cardiovascular risk and in whom an intensive lipid profile intervention was likely to be applied, the additional benefit of homocysteine lowering might be difficult to demonstrate. On the other hand, a meta-analysis of prospective observational studies did not adjust for HDL cholesterol levels, and it is likely to overestimate the association of homocysteine and cardiovascular disease.7

Some limitations of our study need to be mentioned. Meta-analysis is retrospective research that can be constrained by the comprehensiveness of searches, methodological rigor of the included studies, and publication bias. We tried to maximize study identification and minimize bias by developing the study protocol a priori, performing a thorough search of several databases, and using explicit criteria for study selection, data collection, and data analysis. An additional limitation of meta-analyses is that they vary with respect to the characteristics of participants, duration and intensity of treatment, the type of cerebrovascular event identified, the expertise of stroke adjudicators, and other design features. However, formal testing did not identify any substantial resulting heterogeneity among trial findings. In conclusion, our meta-analysis of completed RCTs did not demonstrate a major benefit of folic acid supplementation in averting stroke. However, potential mild benefits were observed in primary stroke prevention, especially when folate was combined with B vitamins and in male patients. Because folic acid supplementation is an inexpensive, safe, and widely applicable intervention, further investigation in these settings is warranted.

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Disclosures
J.L.S. has received honoraria from universities as a visiting professor; is an employee of the University of California, which holds a patent on retriever devices for stroke; is a scientific consultant regarding trial design and conduct to Concentric Medical, Telecres, and Ev3; is a site investigator in multicenter trials sponsored by Lundbeck, for which the University of California Regents received payments based on the clinical trial contracts for the number of subjects enrolled; is a site investigator in the National Institutes of Health IMS 3 and CLEAR-ER multicenter clinical trials for which the University of California Regents received payments based on the clinical trial contracts for the number of subjects enrolled; and has declined consulting/honoraria monies from Genentech since 2002. All other authors report no conflicts of interest.

References
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Abstract

急性缺血性脑卒中溶栓治疗在全国的普及情况：
瑞典卒中登记 2003-2008 年的经验

Dissemination of Thrombolysis for Acute Ischemic Stroke Across a Nation:
Experiences From the Swedish Stroke Register, 2003 to 2008

Meng Lee, MD; Keun-Sik Hong, MD, PhD; Shen-Chih Chang, PhD; Jeffrey L. Saver, MD

背景和目的：我们根据瑞典卒中登记Riks-Stroke的数据，分析自2003年瑞典批准溶栓以来，溶栓治疗在瑞典医院的普及情况。

方法：Riks-Stroke登记了瑞典所有78家医院的急性卒中住院患者。2003-2008年期间，共登记72 033例成人急性缺血性脑卒中住院患者。我们根据地区、患者特征和医疗机构性质分析溶栓的使用情况。

结果：瑞典全国范围内的溶栓率在2003年是0.9%，截至2008年提高到6.6%。瑞典的溶栓普及存在明显的地区差异，但是该差异在逐渐减少。尽管卒中医院的溶栓治疗水平与大学医院类似，但溶栓在非除卒中医院的普及要好2-3年。在溶栓普及过程中，症状性颅内出血发生率保持在3%-9%，未呈现明显的增加趋势。年轻患者、男性、与他人一起生活、无卒中或糖尿病史是高溶栓率的独立预测因素，2008年，入住卒中单元患者接受溶栓的几率是入住普通病房患者的5倍。

结论：虽然溶栓在瑞典的普及较慢，但它普及速度已经逐渐加快，主要归因于非大学医院溶栓比率增加。在溶栓普及过程中，安全地实现了溶栓率的提高，但是患者接受溶栓的机会尚不平等。

关键词：急性缺血性脑卒中，实施，溶栓

(Stroke. 2010;41:1115-1122. 张灿飞 译 刘鸣 郝子龙 校)

叶酸降低同型半胱氨酸的治疗在卒中预防中的效果：Meta 分析

Efficacy of Homocysteine-Lowering Therapy With Folic Acid in Stroke Prevention
A Meta-Analysis

Meng Lee, MD; Keun-Sik Hong, MD, PhD; Shen-Chih Chang, PhD; Jeffrey L. Saver, MD

背景和目的：虽然流行病学研究发现低血清同型半胱氨酸浓度与卒中风险的降低有相关性，但是降同型半胱氨酸治疗预防卒中的随机对照试验却未能取得一致的结果。我们进行一个随机对照试验的Meta分析，以评估补充叶酸在预防卒中上的效果。

方法：通过正式文献搜索确定重要的试验。采用相对危险度及其95%可信区间衡量补充叶酸和卒中风险之间的联系程度。汇总各试验资料后用固定效应模型分析。

结果：检索出符合条件的包括39 005个患者的13个随机对照试验，采用叶酸降低同型半胱氨酸治疗，以卒中作为结局指标，在所有试验中，补充叶酸在卒中预防方面趋向于轻度有效，但未达统计学意义(RR=0.93；95% CI, 0.85-1.03；P=0.16)。在非二级预防的试验中相对危险度是0.89(95% CI, 0.79-0.99；P=0.03)。分层分析发现叶酸治疗在以下试验中疗效较显著：联合叶酸和维生素B6、B12治疗的试验(RR=0.83；95% CI, 0.71-0.97；P=0.02)，以及纳入较多男性患者的试验(男性:女性>2；RR=0.84；95% CI, 0.74-0.94；P=0.003)。

结论：目前暂无证据显示补充叶酸对卒中预防起重要作用，但是在卒中一级预防上有轻度益处，尤其是叶酸和B族维生素联合治疗以及针对男性患者的治疗，值得进一步研究。

关键词：同型半胱氨酸，叶酸，卒中，预防，Meta分析

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