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Folic Acid Therapy Reduces the First Stroke Risk Associated With Hypercholesterolemia Among Hypertensive Patients

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Background and Purpose—We sought to determine whether folic acid supplementation can independently reduce the risk of first stroke associated with elevated total cholesterol levels in a subanalysis using data from the CSPPT (China Stroke Primary Prevention Trial), a double-blind, randomized controlled trial.

Methods—A total of 20 702 hypertensive adults without a history of major cardiovascular disease were randomly assigned to a double-blind daily treatment of an enalapril 10-mg and a folic acid 0.8-mg tablet or an enalapril 10-mg tablet alone. The primary outcome was first stroke.

Results—The median treatment duration was 4.5 years. For participants not receiving folic acid treatment (enalapril-only group), high total cholesterol (≥200 mg/dL) was an independent predictor of first stroke when compared with low total cholesterol (<200 mg/dL; 4.0% versus 2.6%; hazard ratio, 1.52; 95% confidence interval, 1.18–1.97; P=0.001). Folic acid supplementation significantly reduced the risk of first stroke among participants with high total cholesterol (4.0% in the enalapril-only group versus 2.7% in the enalapril–folic acid group; hazard ratio, 0.69; 95% confidence interval, 0.56–0.84; P<0.001; number needed to treat, 78; 95% confidence interval, 52–158), independent of baseline folate levels and other important covariates. By contrast, among participants with low total cholesterol, the risk of stroke was 2.6% in the enalapril-only group versus 2.5% in the enalapril–folic acid group (hazard ratio, 1.00; 95% confidence interval, 0.75–1.30; P=0.982). The effect was greater among participants with elevated total cholesterol (P for interaction=0.024).

Conclusions—Elevated total cholesterol levels may modify the benefits of folic acid therapy on first stroke. Folic acid supplementation reduced the risk of first stroke associated with elevated total cholesterol by 31% among hypertensive adults without a history of major cardiovascular diseases.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00794885.

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Key Words: cholesterol ■ folic acid ■ hypercholesterolemia ■ risk factors ■ stroke

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Hypercholesterolemia is a recognized risk factor for stroke. There is a considerable interest in the efficacy of folic acid therapy in lowering the risk of stroke associated with hypercholesterolemia. In the HOPE-2 trial (Heart Outcomes Prevention Evaluation 2),[1] high total cholesterol (TC) levels were associated with an increased risk of stroke in the placebo group (6.6% versus 3.9%; $P<0.01$). Consistently, folic acid therapy showed a trend toward a greater benefit in reducing stroke among patients with higher baseline TC levels than among patients with lower baseline TC levels (P for interaction=0.34). A meta-analysis[2] of 15 randomized controlled trials found that folic acid supplementation reduced the risk of stroke by 8% on average (relative risk [RR], 0.92; 95% confidence interval [CI], 0.86–1.00), but the effect was greater among those trials with a lower percent use of statins (RR, 0.77; 95% CI, 0.64–0.92), suggesting that the benefits of folic acid supplementation in the prevention of stroke might be hindered by concomitant use of statins because of the possibility of overlapping biological mechanisms.

Although it is plausible that folic acid therapy may lower the risk of stroke associated with hypercholesterolemia, particularly in patients not taking statins, to date, this hypothesis has not been tested in randomized trials. Indeed, hypertension is recognized as a major and modifiable risk factor of stroke. Furthermore, hypertension and elevated homocysteine concentrations have shown a multiplicative effect on cardiovascular disease risk.[3,4] We chose to carry out the trial in Chinese hypertensive patients because we speculated that hypertensive adults in regions without mandatory folic acid fortification may particularly benefit from homocysteine-lowering therapy along with antihypertension therapy. Therefore, the CSPPT (China Stroke Primary Prevention Trial), a multicommunity, double-blind, randomized controlled trial, compared the efficacy of a combination of the angiotensin-converting enzyme inhibitor enalapril and folic acid with enalapril alone in reducing the risk of first stroke in Chinese adults with hypertension.[5] This report, a subanalysis using data from the CSPPT (see the Statistical Analysis Plan of the CSPPT),[5] sought to determine whether folic acid supplementation can independently reduce the risk of first stroke associated with elevated TC levels. A unique aspect of the CSPPT is the low percentage of concomitant use of lipid-lowering drugs (0.8%) at baseline among the study participants, offering an opportunity to determine the independent and interactive effects of folic acid supplementation with elevated TC on first stroke without confounding by statins.

Methods

The methods and primary results of the CSPPT trial have been reported elsewhere.[5] Briefly, a total of 20 702 hypertensive adults without a history of major cardiovascular disease were randomly assigned to a double-blind daily treatment of an enalapril 10-mg and a folic acid 0.8-mg tablet or an enalapril 10-mg tablet alone. Participants were scheduled for follow-up every 3 months.

This study was approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number: FWA00001263). All participants gave written informed consent.

Outcomes

The primary outcome was first stroke. The secondary outcomes included first ischemic stroke (fatal or nonfatal), first hemorrhagic stroke (fatal or nonfatal), and a composite of cardiovascular events consisting of cardiovascular death, myocardial infarction, and stroke.

Statistical Analysis

Means (SD) or medians (25th percentile, 75th percentile) and proportions were calculated for population characteristics by the treatment groups in accordance with baseline TC strata (≥200 versus <200 [desirable levels][6] mg/dL). Low-density lipoprotein cholesterol (LDL-C) was estimated by the Friedewald formula[6] as follows: LDL-C, mg/dL=TC−(high-density lipoprotein cholesterol [HDL-C])−(triglycerides/5).

The hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of the primary outcome associated with elevated TC levels (≥200 versus <200 mg/dL) were estimated using Cox proportional hazards models stratified by treatment groups with adjustment for major covariates.

We further assessed the effect of folic acid supplementation on the prevention of study outcomes according to different TC strata, as well as assessed the interaction between baseline TC strata and folic acid therapy on the study outcomes by means of Cox proportional hazards regression both before and after adjustment for the major covariates. Interactions were examined by including interaction terms in the Cox models.

A 2-tailed $P<0.05$ was considered to be statistically significant in all analyses. R software, version 3.2.0 (http://www.R-project.org/) was used for all statistical analyses.

Results

Study Participants and Baseline Characteristics

The total sample of the CSPPT was 20 702. Of these, 166 participants who were taking lipid-lowering medications and 370 participants who were missing TC data at baseline were excluded from the analysis. A total of 20 166 participants were included in the final analysis (Figure I in the online-only Data Supplement).

At baseline, 11 862 participants (58.8%) had high TC levels (≥200 mg/dL), 8304 participants (41.2%) had low TC levels (<200 mg/dL). Although there were significant differences in baseline characteristics between participants with low TC levels (<200) and with high TC levels (≥200 mg/dL; Table I in the online-only Data Supplement); all of the baseline characteristics were comparable between the 2 treatment groups within each baseline TC strata, with the exception of a higher use of antiplatelet drugs in the enalapril-only group among participants with high TC levels (Tables 1 and 2).

Effects of Folic Acid Therapy on Serum Folate, Blood Pressure, and TC Levels

Table 2 shows that compared with the enalapril-only group, the enalapril–folic acid group showed significantly increased serum folate concentrations. However, there were no significant group differences in TC, systolic blood pressure, or diastolic blood pressure levels both at baseline and after treatment within each baseline TC strata.

We found that mean folate levels in the enalapril-only group also increased substantially ≈54% during the course of the trial. The cause of this increase is unclear. During the course of the study, subjects received nutritional health education,

Table 1. Baseline Characteristics of Participants by Treatment Groups for Baseline Total Cholesterol Strata*

	Total Cholesterol<200 mg/dL			Total Cholesterol≥200 mg/dL		
	Enalapril	Enalapril–Folic Acid	*P* Value	Enalapril	Enalapril–Folic Acid	*P* Value
n	4187	4117		5899	5963	
Male, n (%)	1933 (46.2)	1946 (47.3)	0.315	2198 (37.3)	2162 (36.3)	0.257
Age, y	60.1±7.7	60.2±7.7	0.633	59.9±7.4	59.9±7.4	0.647
Body mass index, kg/m^2	24.3±3.7	24.3±3.7	0.744	25.3±3.6	25.4±3.6	0.364
Methylenetetrahydrofolate reductase C677T polymorphisms, n (%)			0.899			0.984
CC	1225 (29.2)	1222 (29.7)		1535 (26.0)	1543 (25.9)	
CT	2046 (48.9)	2006 (48.7)		2905 (49.3)	2942 (49.3)	
TT	916 (21.9)	889 (21.6)		1459 (24.7)	1478 (24.8)	
Current smoking	1032 (24.6)	1083 (26.3)	0.080	1311 (22.2)	1309 (22.0)	0.728
Current alcohol drinking	960 (22.9)	960 (23.3)	0.679	1470 (24.9)	1434 (24.1)	0.545
Physical activity			0.621			0.881
Low	1323 (31.6)	1342 (32.6)		2331 (39.6)	2331 (39.2)	
Medium	1730 (41.4)	1675 (40.7)		2298 (39.0)	2331 (39.1)	
High	1131 (27.0)	1097 (26.7)		1262 (21.4)	1292 (21.7)	
Self-reported hyperlipidemia	86 (2.1)	80 (1.9)	0.718	160 (2.7)	176 (3.0)	0.432
Self-reported diabetes mellitus	105 (2.5)	112 (2.7)	0.544	210 (3.6)	192 (3.2)	0.306
Laboratory results						
Triglycerides, mg/dL	133.3±79.1	133.9±88.1	0.734	155.9±82.2	156.5±137.3	0.778
HDL cholesterol, mg/dL	47.9±12.3	48.0±12.5	0.561	54.8±14.3	54.9±14.3	0.609
Fasting glucose, mmol/L	5.5±1.4	5.5±1.4	0.451	6.0±1.9	6.0±1.8	0.278
Homocysteine, μmol/L†	12.4 (10.4, 15.4)	12.5 (10.4, 15.6)	0.236	12.6 (10.5, 15.5)	12.6 (10.5, 15.5)	0.444
Vitamin B12, pg/mL†	367.0 (303.6, 463.5)	367.0 (303.9, 460.1)	0.773	388.5 (324.3,487.9)	387.9 (319.8,484.9)	0.139
Medication use, n (%)						
Antihypertensive drugs (all types)	1915 (45.7)	1838 (44.6)	0.317	2739 (46.4)	2730 (45.8)	0.478
Antihypertensive drugs (subtypes)						
Angiotensin-converting enzyme inhibitors	399 (9.5)	392 (9.5)	0.990	524 (8.9)	513 (8.6)	0.590
Angiotensin II–receptor blockers	2 (0.1)	4 (0.1)	0.402	6 (0.1)	4 (0.1)	0.516
Calcium channel blockers	490 (11.7)	485 (11.8)	0.913	517 (8.8)	522 (8.8)	0.984
Diuretics	68 (1.6)	63 (1.5)	0.732	140 (2.4)	143 (2.4)	0.929
β-Blockers	41 (1.0)	28 (0.7)	0.133	44 (0.7)	54 (0.9)	0.337
Glucose-lowering drugs	44 (1.1)	55 (1.3)	0.232	94 (1.6)	103 (1.7)	0.569
Antiplatelet drugs	94 (2.2)	92 (2.2)	0.974	203 (3.4)	166 (2.8)	0.039

HDL indicates high-density lipoprotein.
*For continuous variables, values are presented as mean±SD.
†Values are medians (25th, 75th percentile), Wilcoxon signed-rank test was used.

which may have led to improved dietary choices. Whatever the cause, this change likely attenuated the beneficial effect.

Interactive Effect of Folic Acid Therapy and TC on First Stroke

Over the median treatment duration of 4.5 years, for participants not receiving folic acid (the enalapril-only group), high baseline TC levels (≥200 versus <200 mg/dL; 4.0% versus 2.6%; HR=1.52; 95% CI, 1.18–1.97; *P*=0.001) were significantly associated with increased risk of first stroke, after adjustment for major covariates (age, sex, MTHFR C677T genotypes, systolic blood pressure and diastolic blood pressure at baseline, mean systolic blood pressure and diastolic blood pressure over the treatment period, body mass index,

Table 2. Serum Folate, Total Cholesterol Levels, and Blood Pressure at Baseline and After Treatment-by-Treatment Groups for Baseline Total Cholesterol Strata*

Variables	Total Cholesterol<200 mg/dL			Total Cholesterol≥200 mg/dL		
	Enalapril	Enalapril–Folic Acid	*P* Value	Enalapril	Enalapril–Folic Acid	*P* Value
Folate, ng/mL						
At baseline	8.2 (5.6, 10.9) [4139]	8.3 (5.6, 10.9) [4081]	0.697	8.0 (5.6, 10.3) [5862]	7.9 (5.6, 10.2) [5910]	0.597
At exit visit	13.1 (9.8, 16.1) [3380]	20.2 (15.2, 23.6) [3350]	<0.001	12.9 (9.6, 15.9) [4806]	19.6 (14.5, 23.2) [4861]	<0.001
Change†	4.3 (1.6, 7.3) [3340]	11.5 (5.9, 17.2) [3319]	<0.001	4.4 (1.7, 7.3) [4777]	11.0 (5.6, 16.6) [4820]	<0.001
Total cholesterol, mg/dL						
At baseline	177.2 (161.0, 190.0) [4187]	176.8 (159.8, 189.6) [4117]	0.133	233.6 (215.8, 258.3) [5899]	234.4 (216.6, 257.9) [5963]	0.386
At exit visit	183.4 (163.3, 204.2) [3393]	181.9 (162.9, 203.9) [3347]	0.489	218.1 (195.4, 244.0) [4905]	218.1 (196.5, 244.4) [4927]	0.617
Change†	8.1 (–9.3, 29.3) [3393]	8.1 (–10.0, 29.3) [3347]	0.974	–19.3 (–42.1, 3.1) [4905]	–19.3 (–42.5, 3.5) [4927]	0.941
Systolic blood pressure, mm Hg						
Baseline	161.3 (151.3, 176.7) [4187]	161.3 (151.3,177.3) [4117]	0.586	166.0 (154.7, 180.0) [5899]	165.3 (154.0, 180.0) [5963]	0.273
Over treatment period	138.0 (131.7, 145.4) [4186]	138.2 (131.6, 145.9) [4117]	0.472	138.9 (132.2, 146.4) [5899]	138.5 (132.1, 145.9) [5963]	0.072
Diastolic blood pressure, mm Hg						
Baseline	92.0 (84.7, 100.0) [4187]	92.7 (85.3,100.0) [4117]	0.053	94.7 (87.3,101.3) [5899]	94.7 (87.3, 101.3) [5963]	0.600
Over treatment period	82.4 (77.4, 87.3) [4186]	82.4 (77.5, 87.5) [4117]	0.996	82.9 (78.4, 87.6) [5899]	82.8 (78.5, 87.5) [5963]	0.559

*Values are medians (25th, 75th) [number of participants with available data].
†Change=exit level (folate or total cholesterol)–baseline level.

study centers, vitamin B12, folate, homocysteine, TG, HDL-C, creatinine, glucose levels, and smoking status). However, the increased risk associated with high TC levels (2.7% versus 2.5%; HR, 1.05; 95% CI, 0.80–1.39; *P*=0.727) was no longer significant in the enalapril–folic acid group (Figure 1). Similar results were found for ischemic stroke (Figure 1).

Kaplan–Meier curves of the cumulative event rate of first stroke and ischemic stroke for the 2 treatment groups within each baseline TC strata are shown in Figure 2. Folic acid therapy did not have a significant effect on risk of first stroke (2.6% in the enalapril-only group versus 2.5% in the enalapril–folic acid group; HR, 1.00; 95% CI, 0.75–1.30; *P*=0.982) in participants with low baseline TC levels (<200 mg/dL). In contrast, among participants with high baseline TC levels (≥200 mg/dL), folic acid therapy significantly reduced the risk of first stroke to a level that was on par with participants with low baseline TC levels (4.0% in the enalapril-only group versus 2.7% in the enalapril–folic acid group; HR, 0.69; 95% CI, 0.56–0.84; *P*<0.001; number needed to treat [4.5 years], 78; 95% CI, 52–158), independent of baseline folate levels and other important covariates listed above. The interaction between baseline TC levels and folic acid therapy on risk of first stroke was significant (*P* for interaction=0.024). The overall results were consistent for ischemic stroke (*P* for interaction=0.035), the composite of stroke, myocardial infarction, or death from cardiovascular causes (*P* for interaction=0.026), and composite of stroke or all-cause death (*P* for interaction=0.038), but not for hemorrhagic stroke (*P* for interaction=0.485; Table 3).

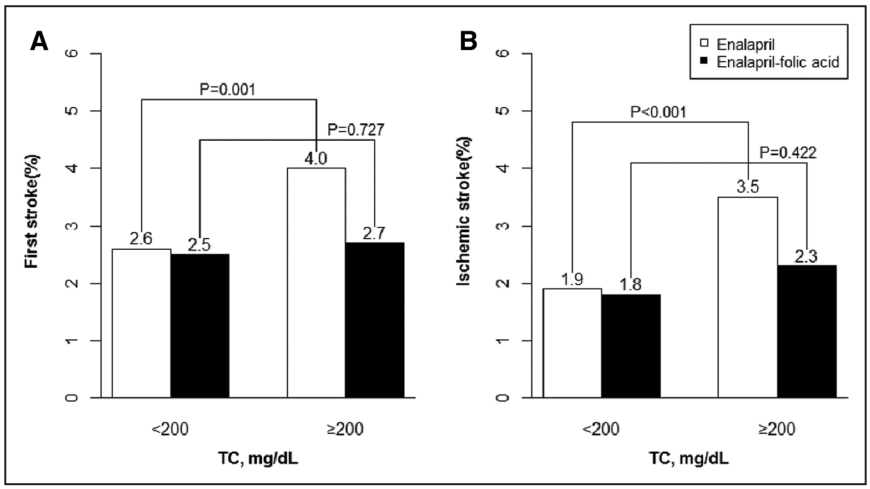

Figure 1. Rates of first stroke (**A**) and ischemic stroke (**B**) by treatment groups and baseline total cholesterol (TC) strata.

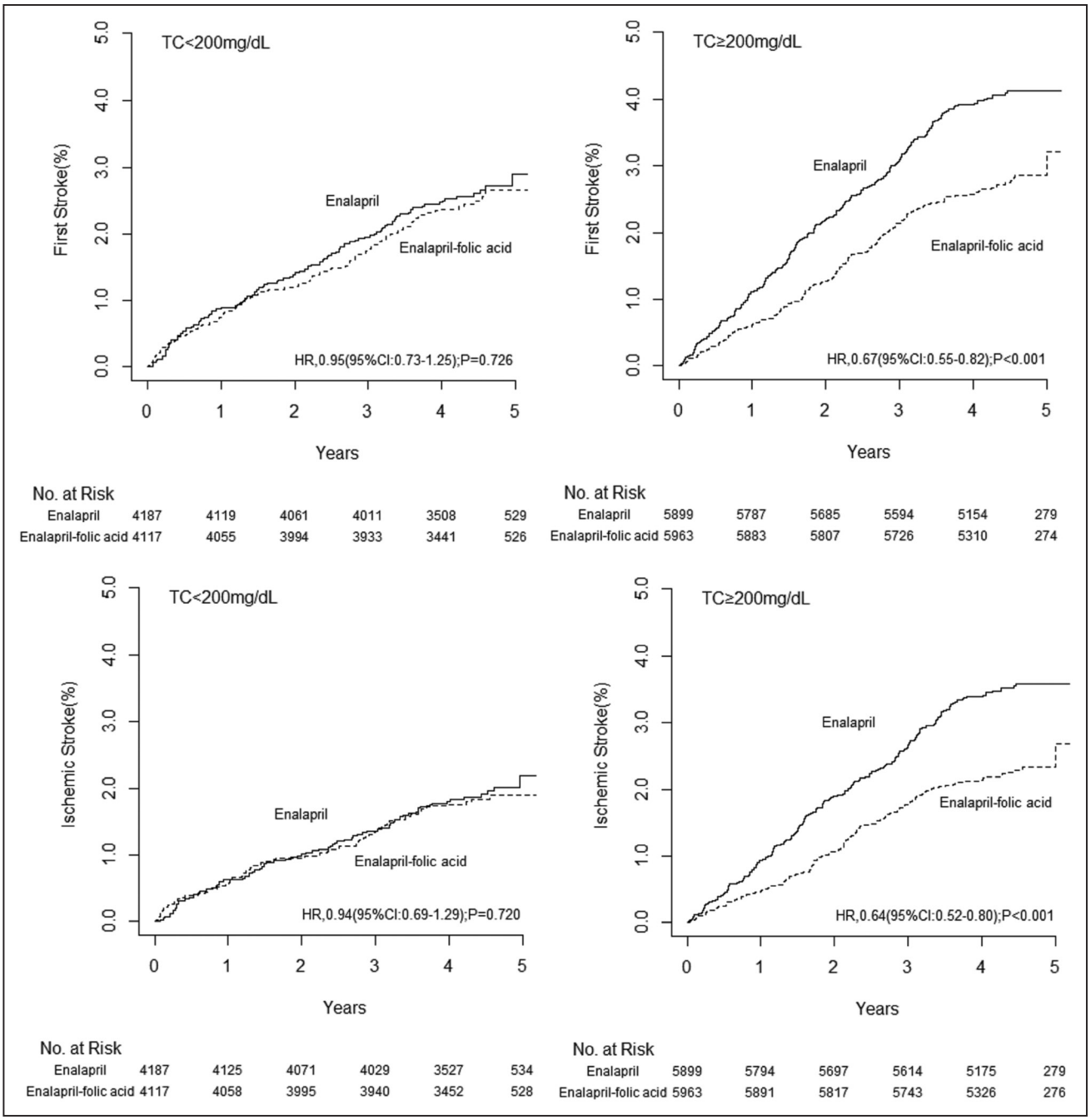

Figure 2. Kaplan–Meier curves of cumulative hazards for first stroke and ischemic stroke within each baseline total cholesterol (TC) strata. CI indicates confidence interval; and HR, hazard ratio.

Similar results were observed between baseline LDL-C levels (≥100 versus <100 [optimal levels][6] mg/dL) and folic acid therapy on incident stroke (Table II in the online-only Data Supplement). Exclusion of participants with LDL-C≥190 mg/dL or diabetes mellitus or fasting glucose ≥7.0 mmol/L at baseline did not change the benefits for participants with high LDL-C levels (LDL-C≥100 mg/dL: HR, 0.76; 95% CI, 0.61–0.93 versus LDL-C<100 mg/dL: HR, 1.32; 95% CI, 0.82–2.12; *P* for interaction=0.032).

The 20th percentiles of LDL-C and TC levels were ≈100 and 177 mg/dL, respectively. Greater beneficial results were also observed in participants with TC≥177 mg/dL (HR, 0.72; 95% CI, 0.61–0.86) versus TC<177 mg/dL (HR, 1.28; 95% CI, 0.83–1.98; *P* for interaction=0.017).

Exploratory Stratified Analyses by Important Covariables

The Table III in the online-only Data Supplement showed that of all the listed subgroups, there was a greater beneficial effect for the enalapril–folic acid group than for the enalapril-only group on risk of first stroke for participants with high TC levels at baseline than those with low TC levels at baseline although many of the comparisons were not statistically significant. Similar results were also observed between baseline

Table 3. Interaction Between Folic Acid Therapy and Total Cholesterol Levels at Baseline on First Stroke

Total Cholesterol, mg/dL	Enalapril		Enalapril–Folic Acid		HR (95% CI)	*P* Value	*P* for Interaction	Adjusted HR* (95% CI)	*P* Value*	*P* for Interaction*
	Total	n (%)	Total	n (%)						
Primary outcome										
First stroke										
<200	4187	109 (2.6)	4117	102 (2.5)	0.95 (0.73–1.25)	0.727	0.044	1.00 (0.76–1.32)	0.982	0.024
≥200	5899	237 (4.0)	5963	163 (2.7)	0.67 (0.55–0.82)	<0.001		0.69 (0.56–0.84)	<0.001	
Secondary outcomes										
Ischemic stroke										
<200	4187	80 (1.9)	4117	74 (1.8)	0.94 (0.69–1.29)	0.720	0.049	0.99 (0.72–1.37)	0.964	0.035
≥200	5899	205 (3.5)	5963	134 (2.3)	0.64 (0.52–0.80)	<0.001		0.66 (0.53–0.82)	<0.001	
Hemorrhagic stroke										
<200	4187	28 (0.67)	4117	28 (0.68)	1.02 (0.60–1.72)	0.947	0.656	1.08 (0.63–1.83)	0.785	0.485
≥200	5899	32 (0.54)	5963	28 (0.47)	0.86 (0.52–1.43)	0.569		0.82 (0.49–1.37)	0.446	
Composite of stroke, myocardial infarction, or death from cardiovascular causes										
<200	4187	126 (3.0)	4117	118 (2.9)	0.95 (0.74–1.23)	0.715	0.035	1.00 (0.77–1.29)	0.998	0.026
≥200	5899	269 (4.6)	5963	187 (3.1)	0.68 (0.57–0.82)	<0.001		0.70 (0.58–0.85)	<0.001	
Sensitivity analyses										
Composite of first stroke or all-cause death										
<200	4187	240 (5.7)	4117	228 (5.5)	0.97 (0.81–1.16)	0.722	0.075	1.02 (0.85–1.23)	0.811	0.038
≥200	5899	385 (6.5)	5963	307 (5.2)	0.78 (0.67–0.91)	0.001		0.79 (0.68–0.92)	0.002	

*Adjusted for age, sex, MTHFR C677T genotypes, study centers, systolic blood pressure, and diastolic blood pressure at baseline, mean systolic blood pressure and diastolic blood pressure over the treatment period, body mass index, baseline laboratory measurements for vitamin B12, folate, homocysteine, triglycerides, high-density lipoproteins cholesterol, creatinine and glucose levels, and smoking status.

LDL-C and folic acid therapy on first stroke in different subgroups (Table IV in the online-only Data Supplement).

Discussion

This study was the first to demonstrate that elevated TC levels modify the benefits of folic acid supplementation on first stroke. Folic acid therapy significantly reduced the risk of first stroke associated with elevated TC levels by 31%, independent of baseline folate levels and other important covariates. Our results have important clinical and public health implications.

Elevated level of TC is a recognized risk factor for stroke and has become a major public health concern throughout the world.[7] From 2011 to 2012, 38.9% of US adults aged 20 to 49 years and 75.8% of US adults aged ≥50 years had TC levels ≥200 mg/dL.[8] In China, from 2000 to 2001, the age-standardized prevalence of high TC levels (≥200 mg/dL) was 32.8% in a nationally representative sample of 15 540 Chinese adults aged 35 to 74 years.[9] In the recently published results of the HOPE-3 study (Heart Outcomes Prevention Evaluation 3), treatment with rosuvastatin[10] resulted in a significantly lower risk of cardiovascular events than placebo in an intermediate-risk, ethnically diverse population without cardiovascular disease. However, although statins are the major class of drug most commonly used to lower cholesterol to prevent cardiovascular diseases including stroke, there are several issues associated with statin use. First, statin intolerance occurs in 10% to 15% of patients.[11] Patients who take statins can experience a series of adverse effects, including myopathy and new-onset diabetes mellitus, which is particularly common in Asian populations.[12,13] The value of other lipid-lowering therapies in patients who cannot tolerate statins in the primary prevention of stroke is uncertain.[14] Second, even among individuals with cardiovascular disease, the usage of statin medication is much lower among middle- to low-income countries: 17.5% in upper middle-income countries, 4.3% in lower middle-income countries, 3.3% in low-income countries, and 1.7% in China, compared with 66.5% in high-income countries.[15] There are >1 billion hypertensive patients worldwide[16] (≈300 million in China[17]). From a public health perspective, in China alone, a 1.3% decrease in absolute stroke risk (number needed to treat=78) associated with folic acid supplementation in patients with hypercholesterolemia could translate into sparing ≈2 million people from stroke >4.5 years. Furthermore, we have shown that folic acid had no adverse effect on tolerability of an enalapril-based antihypertensive treatment.[5]

The recommendations of statin medications for the primary prevention of cardiovascular diseases vary substantially among several recently published guidelines. According to 2013 guidelines produced the American College of Cardiology/American Heart Association,[18] for primary prevention, statin medications should be initiated for individuals with primary elevations of LDL-C≥190 mg/dL, diabetes mellitus, or an estimated 10-year cardiovascular events risk of ≥7.5%. Our results showed that after excluding participants

with LDL-C≥190 mg/dL or diabetes mellitus at baseline, we still found significantly beneficial results from folic acid supplementation for participants with LDL-C≥100 mg/dL but <190 mg/dL. Furthermore, the beneficial effects were consistent in participants with relatively lower cardiovascular risk, such as younger patients, women, or those with lower glucose levels or lower blood pressure at both baseline and during the treatment period. These results suggest that folic acid supplementation may possibly have a role in the primary prevention of stroke among individuals with relatively low estimated risk for cardiovascular events.

Hypercholesterolemia may influence 3 aspects important to atherothrombosis: endothelial function, platelet aggregation (primary coagulation), and secondary coagulation.[19] Consistently, several studies have demonstrated that folic acid ameliorates endothelial dysfunction and nitrate tolerance and can improve pathological features of atherosclerosis.[20] Folic acid also has a potent homocysteine lowering effect, as well as direct antioxidant and antithrombotic effects.[21] In fact, the potential mechanisms underlying the benefits of statins are similar and also include improved endothelial dysfunction and a positive effect on the fibrinolytic system and platelet function.[22] Our findings should stimulate further investigation into the mechanisms underlying the interactive effect of folic acid and high TC on stroke. This line of further research may provide new insights into the pathogenesis of stroke and inform novel preventive and treatment strategies for stroke.

Inadequate folate intake is prevalent in most countries lacking mandatory folic acid fortification of foods, including Asia and other continents. In the CSPPT, a folic acid dose of 0.8 mg/d, the ceiling dose[2] of folic acid supplementation in reducing stroke, was used. In the United States, after the introduction of folic acid fortification of food, total folic acid intake was only ≈250 to 400 μg/d in women and 300 to 420 μg/d in men.[23] From 2003 to 2004, the median serum folate concentration in the United States was ≈11.9 ng/mL[24] (versus 19.9 ng/mL in the CSPPT after treatment). Therefore, we speculate that even in countries such as the United States and Canada, where folic acid fortification and use of folic acid supplements are widespread, there may still be room to further reduce stroke risk by introducing a target-specific folic acid therapy for those individuals with hypercholesterolemia. Folic acid is attractive because it is safe and inexpensive. We think that that our findings on the effects of folic acid supplementation on the risk of first stroke associated with hypercholesterolemia have implications for hypertensive adults across the globe.

This is a subanalysis of the CSPPT for the primary outcome. The systematic bias in treatment allocation was minimized by the randomized process. The observer bias in the assessment of first stroke was minimized by masking the treatment allocation from investigators, participants, and the independent end point adjudication committee. Random error was reduced by the reasonably large number of outcome events.

Several potential concerns or limitations are worth mentioning. First, one should note that subanalyses of randomized trials have inherent limitations, such as the possibility of residual imbalance in some unmeasured predictive factors at baseline. However, the distribution of important covariables was comparable between treatment groups within each baseline TC strata. Second, this study focused on the primary prevention of stroke in hypertensive adults; the generalizability of our findings to the secondary prevention of stroke or in populations with a high percent use of statins remains to be determined. Third, previous studies have reported that antiplatelet therapy possibly modifies the potential benefits of folic acid supplementation in the secondary prevention of vascular events.[25] In the CSPPT study, only ≈3% of the participants were exposed to antiplatelet drugs; this number is too small for any meaningful analysis of the possible interaction between antiplatelet drugs and the effect of folic acid therapy on the primary prevention of stroke. Fourth, in the CSPPT, the stroke was not quantified using National Institute of Health Stroke Scale. Therefore, we could not evaluate the association between folic acid supplementation and risk of moderate-to-severe stroke. Another limitation of the CSPPT is the lack of classification of subtypes of ischemic stroke based on mechanisms such as the Trial of ORG 10172 in Acute Stroke Treatment classification. In addition, C-reactive protein was not measured at baseline and could not be included in the multivariable models as a potential confounder. Therefore, we cannot rule out the possibility of residual confounders. More importantly, statistical power was calculated for the main effect (the primary objective) of the CSPPT. All the subgroup analyses were exploratory without taking multiple testing into consideration. Therefore, our results are hypothesis generating. Confirmation of our findings in an independent population is essential.

Conclusions

Among hypertensive patients without a history of major cardiovascular diseases in China, elevated TC levels modified the benefits of folic acid supplementation on risk of first stroke. Folic acid supplementation reduced the risk of first stroke associated with elevated TC levels by 31%, independent of baseline folate levels and other important covariates. If confirmed by further studies, high TC may serve as an indicator for folic acid supplementation or higher folate intake in the primary prevention of stroke in hypertensive patients, particularly those who do not have access to statins (populations from low-income countries).

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Disclosures

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