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Hypertension. Author manuscript; available in PMC 2021 April 05.

Published in final edited form as:

Hypertension. 2020 February ; 75(2): 339–346. doi:10.1161/HYPERTENSIONAHA.119.14102.

Estimated Stroke-Free Survival of Folic Acid Therapy for Hypertensive Adults Projection Based on the CSPPT

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The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.119.14102.

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Abstract

The CSPPT (China Stroke Primary Prevention Trial) demonstrated a significant risk reduction of first stroke in hypertensive patients treated with enalapril plus folic acid compared with those with enalapril alone, but the lifetime stroke-free survival associated with the treatment is unknown. By establishing adjusted models for competing risks and an age-based time scale using data from 19053 participants of the CSPPT, we estimated lifetime incremental stroke-free survival for enalapril-folic acid versus enalapril alone. Compared with enalapril alone, the enalapril plus folic acid treatment projected a mean lifetime stroke-free survival gain of 1.75 months, with an interquartile range from 0.73 to 2.39 months and the maximum gain up to 12.95 months. Subgroup analyses showed greater gain in stroke-free survival in younger, male patients, those with lower baseline folate levels, higher baseline systolic blood pressure, higher baseline total cholesterol and blood glucose, and with MTHFR (methylenetetrahydrofolate reductase) C677T CT or TT genotype. Overall, besides significant benefit in certain subgroups, enalapril plus folic acid treatment for hypertensive patients is associated with a modest gain in lifetime stroke-free survival, compared with enalapril alone.

Keywords

folic acid; hypertension; life expectancy; primary prevention; stroke

Stroke has been among the leading cause of mortality and serious, long-term disability in the world and China.[1–4] Notably, as >75% of strokes are first occurrence,5 it is imperative to seek an effective strategy for primary prevention of stroke in China and around the world.

The role of supplemental folic acid therapy in cardiovascular disease (CVD) and stroke prevention has remained controversial.[6–9] The CSPPT (China Stroke Primary Prevention Trial)[10] demonstrated that enalapril-folic acid was more effective in first stroke prevention than enalapril alone among hypertensive patients, with a reduction of 21% in first stroke incidence. Recently, meta-analyses on various populations reported the consistent effect of folic acid in risk reduction of CVD, including stroke.[11–13]

Since the CSPPT and other trials only followed patients for a limited time period, it is unknown whether folic acid supplementation combined with antihypertensive treatment is a superior strategy than the antihypertensive strategy alone over a lifetime, given that hypertension is a chronic condition and requires a lifetime treatment. In addition, it is also of

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great interest to clarify whether the lifetime benefit varies by patients' clinical and demographic characteristics. Such information is critically needed to inform clinical and public health practice and health policy, given millions of hypertensive patients who might benefit from this therapy. In this study, we performed a lifetime stroke-free survival projection of the treatment effect of enalapril plus folic acid compared with enalapril alone based on empirical data from the CSPPT.

Methods

Availability of Data and Materials

The data, analytic methods, and study materials that support the findings of this study will be available from the corresponding authors on request after the request is submitted and formally reviewed and approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University.

Standard Protocol Approvals, Registrations, and Patient Consents

We used the data from the CSPPT, which was approved by the ethics committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number FWA00001263). All patients provided written informed consent. The CSPPT is registered at the National Institutes of Health website (http://www.clinical-trials.gov) as identifier NCT00794885.[10]

Summary of the CSPPT

The details of the CSPPT have been published elsewhere.[10] Briefly, the CSPPT was a randomized, double-blind clinical trial with the primary focus of comparing the effects of 10 mg enalapril combined with 0.8 mg folic acid daily therapy (single-pill compound, the enalapril-folic acid group) with 10 mg enalapril daily therapy alone (the enalapril group) on first stroke prevention. The CSPPT enrolled 20702 hypertensive adults without history of stroke or MI (myocardial infarction) in 32 communities in Anhui and Jiangsu provinces in China between May 19, 2008 and August 24, 2013. The participants enrolled in this trial were aged 45 to 75 years with hypertension defined as seated resting systolic blood pressure (SBP) higher than 140 mm Hg, or diastolic blood pressure (DBP) higher than 90 mm Hg at both the screening and recruitment visits or, who were receiving antihypertensive medication. The primary outcome was the first nonfatal or fatal stroke (ischemic or hemorrhagic), excluding subarachnoid hemorrhage and silent stroke. After a mean follow-up of 4.5 years, the hazard ratio for occurrence of the primary outcome was 0.79 (95% CI, 0.68–0.93), favoring the enalapril-folic acid group.

Competing Risk Regression Model and Estimation of Gain in Stroke-Free Survival

We used a competing risk-adjusted lifetime model based on a left truncation and right censoring model, as well as adaptations from the Fine and Gray model, which yielded cause-specific estimates of the cumulative incidence of 2 competing end points, first stroke, and nonstroke death.[14–19] To make a lifetime stroke-free survival projection, we used patient age as the time scale to account for the limited follow-up time of the CSPPT.[19] By estimating survival functions and parameters (β-coefficients, baseline cumulative sub-hazard functions,

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age-based cumulative sub-hazard functions, cumulative incidence functions, etc), we projected annual rates of stroke-free survival for each patient, by which we could fit the predicted stroke-free survival curve for each patient throughout the patient's lifetime. By calculating the area under the stroke-free survival curve, we were able to project stroke-free survival for each patient. We then established a prediction model which estimated the projection of a stroke-free survival for each patient according to their clinical and demographic characteristics.[19] In our model, each patient performed one of the 2 treatment scenarios (enalapril versus enalapril-folic acid). The difference in each patient's stroke-free survival under these 2 scenarios was considered as the patient's clinical benefit. More details are described in the online-only Data Supplement.

Means and standard deviations and proportions were calculated for population characteristics by quartiles of the incremental stroke-free survival. Differences in population characteristics were compared using ANOVA for continuous variables or χ^2tests for categorical variables, respectively. Multivariable linear regression models and logistic model were performed to determine the association between the incremental stroke-free survival with main risk factors. All analyses were adjusted for age, sex, MTHFR (methylenetetrahydrofolate reductase) C677T genotype, baseline SBP and DBP, mean SBP and DBP during treatment, body mass index, treatment group, study center, baseline serum folate, vitamin B12, fasting glucose, total cholesterol, triglycerides, HDL-C (high-density lipoprotein cholesterol), homocysteine, creatinine levels, smoking status, and alcohol drinking status.

Subgroup Analysis

We performed prespecified subgroup analysis of stroke-free survival according to a selected combination of risk factors strata, including age, sex, SBP at baseline, total cholesterol, fasting glucose, MTHFR C677T polymorphism, and folate levels.

The establishment of first stroke and nonstroke death competing model, calculation of baseline cumulative sub-hazard functions of 2 competing end points, and β-coefficients for the model were conducted using STATA (Version 14.0; StataCorp College Station, TX).[20] Estimation of other survival functions and parameters, calculation of area under survival curve, and other calculations were all conducted using R software packages (version 3.5.3. http://www.r-project.org, packages: survival, LifeTables, and demography).

Results

Characteristics of the Study Population

A flow chart of participants who were included in the analyses is presented in the Figure S1 in the online-only Data Supplement. Among the original 20702 CSPPT participants, 588 were excluded due to missing data of one or more covariates. An additional 1061 individuals were removed due to age <47 years old. Baseline characteristics of the final sample of 19053 participants are shown in Table 1. The mean age of the participants was 60.8 (SD 7.0) years, and 41.1% were male, with 23.7% being active smoker and 24.0% consuming alcohol. The mean baseline SBP and DBP was 167.2 (SD 20.4) and 93.7 (SD 11.8) mm Hg, respectively,

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while mean SBP and DBP during treatment period was 139.4 (SD 10.8) and 82.6 (SD 7.2) mm Hg (Table 1).

Model Establishment

We used the 19053 participants for the development of an age-based cumulative sub-hazard function of stroke and nonstroke death, respectively. Based on these function parameters, we established a projection model for participants at entry age up to an exit age of 80. In this model, we evaluated the lifetime benefit from the folic acid therapy versus without the folic acid therapy. The β-coefficients and *P* values of the projection models for first stroke-risk and nonstroke death are presented in Table 2.

Baseline SBP (β=0.0136, $P<0.001$), fasting glucose (β=0.1022, $P<0.001$), mean DBP during treatment period (β=0.0325, $P=0.001$), together with smoking status and total cholesterol, were the statistically significant predictors of for first stroke to estimate stroke-free survival. The enalapril plus folic acid treatment was associated with a significantly lower risk for first stroke (β=−0.2440, $P=0.003$) and eventually increasing stroke-free survival.

For nonstroke death, the statistical significant predictor were mean SBP during treatment period (β=0.0291, $P<0.001$), body mass index (β=−0.0631, $P<0.001$), creatinine (β=0.0060, $P<0.001$), fasting glucose (β=0.1036, $P<0.001$), as well as homocysteine, total cholesterol, and triglycerides. It is noted that treatment with enalapril plus folic acid was not significantly associated with a lower risk for nonstroke death.

Gains in Stroke-Free Survival

Compared with the enalapril alone therapy, the enalapril-folic acid therapy prolonged lifetime stroke-free survival by mean of 1.75 months (95% CI, 1.73–1.77 months), median gain of 1.42 months, an interquartile range from 0.73 months to 2.39 months with a maximum gain up to 12.95 months (Figure S2). As shown, Figure 1 illustrates the cumulative survival free of stroke and death for a 47-year-old male with diabetes mellitus (fasting blood glucose level of 7.86 mmol/L), total cholesterol level of 8.14 mmol/L, folate level of 2.74 ng/mL, and baseline SBP of 185 mm Hg. The effect of enalapril-folic acid compared with enalapril alone is represented by the size of the light blue area between the curves; for this patient, the gain is equal to 7.92 months.

Baseline characteristics of the participants according to quartiles of incremental stroke-free survival are presented in Table 3. Participants with higher predicted folic acid treatment effect tended to have younger age, higher body mass index, higher SBP and DBP, higher total cholesterol, higher glucose and lower folate concentrations, and were more likely to be current smokers and alcohol drinkers and the MTHFR C677T CT or TT genotype carrier (Table 3). These patterns remain after adjusting for potential covariates (Table S1 and Figure S3).

Subgroup Analysis by Risk Factors

The gains in stroke-free survival by the enalapril-folic acid therapy were categorized according to combined selected risk factors (Figure 2). Up to a mean of 5.3 months of

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stroke-free life years could be achieved in male patients with baseline SBP higher than 180 and age younger than 55. Up to a mean of 4.2 months of stroke-free life years could be gained in patients with glucose higher than 7.0 mmol/L while total cholesterol higher than 6.2 mmol/L as well as age younger than 55. A mean of 3.4 months of stroke-free life years could be gained in patients whose folate level were <5.6 ng/mL with MTHFR C677T TT genotype as well as age younger than 55.

Discussion

This study attempted to address a critically needed public health and policy question related to primary prevention of stroke in China, a country with the largest burden of stroke in the world. First, the CSPPT primary results were limited to the estimation of folic acid efficacy during the clinical trial period (an average of 4.5 years).[10] We, for the first time, estimated the lifetime benefit of enalapril plus folic acid treatment compared with enalapril alone in the primary prevention of stroke via assessing stroke-free survival. This is important, given hypertension requires life-long treatment. Second, the primary results focused on the risk of incident stroke, while this study focused on stroke-free survival, an important parameter of health economics. Third, our analyses lent further support for the CSPPT primary findings and post hoc analyses[10,21–23] that certain subgroups appeared to have greater reduction in stroke risk in response to folic acid therapy. Consistently, this study showed a greater gain in lifetime stroke-free survival with the folic acid therapy in certain subgroups, including younger males, those with lower baseline folate levels, and those with higher levels of SBP, total cholesterol, and fasting glucose, or those with MTHFR C677T CT or TT genotype.

Our subgroup analyses suggested that patients with low folate baseline level may have longer lifetime stroke-free survival from folate therapy. This helps to explain why most folate trials among western countries such as the United States were negative, where the proportion of individuals with very low folate levels (<3 ng/mL) has decreased substantially from 22% to 1.7% and mean folate levels increased from 4.6 ng/mL to 11.9 ng/mL after the mandatory folate fortification of grain products (implemented since 1998 to reduce incidence of neural tube defects).[24,25] However, even in the United States, Asian Americans have a higher mortality, prevalence, and incidence of stroke and more severe stroke complications than whites.[26,27] We speculate that folic acid therapy may benefit those Asian Americans, especially among first-generation immigrants, with MTHFR 677 TT genotype and low folate levels, even though United States is the country with mandatory folic acid fortification. More importantly, besides people living in China, large parts of the world's population in Bangladesh and Scandinavia,[28] whose mean folate level may be as low as 6.1 nmol/L with 89.2% of local males in spring suffering from inadequate folate intake,[29] and those populations in low folate regions may potentially benefit from folate supplementation. However, whether our findings can be readily extrapolated to other populations with different genetic, nutritional, and clinical characteristics will require further research.

Our findings seem to be biologically plausible. Previous biochemical and pathological studies have showed that elevated total homocysteine could induce vascular disease, and the main mechanisms involve impaired endothelial function, increased oxidative stress, alterations of lipid metabolism, and induction of thrombosis.[30] Hypertension and elevated

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homocysteine are both independent, modifiable risk factors, which were proven to act additively to increase the risk of first stroke and stroke mortality.[31,32] Folate is considered as one of the most important dietary determinants of homocysteine,[33] which acts as substrates in the metabolism of methionine and homocysteine.[34] The C→T mutation of MTHFR C677T leads to a reduction in enzyme activity for folate metabolism, resulting in decreased blood folate levels and increased blood homocysteine levels.[34] The CSPPT primary results and its post hoc studies have also demonstrated that baseline serum folate levels and the MTHFR C677T genotype could jointly modify the folic acid therapeutic effect on serum homocysteine lowering and primary prevention of stroke.[10]

While our estimated incremental stroke-free survival for enalapril-folic acid appears to be modest, it is comparable to previous studies in CVD. Using the same method as our study, Dorresteijn[19] showed that most of participants from the Women's Health Study[35,36] (94%) had a predicted aspirin treatment effect of <2 months gain in CVD-free survival compared with those without aspirin treatment. Ferket et al[37] predicted that the mean increased CHD/stroke-free survival was 8.4 months with statin therapy compared with no therapy for asymptomatic individuals. Of note, the aforementioned studies on the lifetime benefits of aspirin and statin were all based on comparison to no therapy, our research on folic acid therapy was compared with standard antihypertensive therapy (enalapril). As enalapril was proven to have significant primary CVD preventive effect than no therapy,[38] it may well be that folic acid therapy coupled with enalapril may have a much longer lifetime stroke-free survival when compared with no therapy among hypertensive patients, but such a study is not possible due to ethical concern.

As for the subgroup analysis of lifetime benefit stratified by patients' characteristics, our findings illustrated those by the Joint British Societies' consensus recommendations for the prevention of CVD,[17] which found that younger patients who had been evaluated with a low 10-year risk were nevertheless proven to have a high lifetime event risk. Additionally, aspirin and statins were proven to have a greater lifetime benefit when the medication was applied at a younger age.[19,37] These findings are consistent with our results in that a younger population could benefit more than an elder population from the folic acid therapy.

Our study has a number of strengths. Methodologically, based on a previously validated method,[19] we converted the original CSPPT data (by far, the world largest randomized double-blind clinical trial for the primary prevention of stroke) into an evaluation of patient-level lifetime stroke-free survival benefit. Our model took competing risks into consideration for long-term projection. Ignoring competing risks may cause an overestimation of the final result.[39] Our study has important clinical and public health implications. We for the first time estimated the lifetime benefit of enalapril plus folic acid treatment compared with enalapril alone in the primary prevention of stroke via assessing stroke-fee survival. Chronic diseases such as hypertension generally require lifetime medications, and evidence for decision-making should reflect the long-term benefit.[17] Such information can facilitate physicians, patients, and policy makers to make informed decisions according to individual characteristics, risk, and benefits of life long hypertension treatment for the prevention of stroke.

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Some limitations in our study are noted. We did not consider the changes in risk factor levels over time, such as age-related changes in blood pressure and cholesterol levels. However, bias may be mitigated because large fluctuations in these biomarkers or risk factors are usually not seen until first CVD event.[17] Second, the effect of folic acid therapy was modeled based on the CSPPT data with stringent inclusion and exclusion criteria that may constrain generalizability of our findings. Due to the fact that there was no occurrence of the end point before age 47 in the CSPPT, our prediction model can only apply to patients aged 47 to 80 years old. Third, although our model for prediction of stroke-free survival is useful, our findings need further validation in independent data sets. Lastly, our study only included Chinese hypertensive patients, whether the findings can be extrapolated to other populations requires further verification.

Perspectives

Based on the CSPPT data, we estimated patient-level lifetime stroke-free survival for the enalapril-folic acid therapy compared with enalapril alone for primary prevention of stroke in hypertensive patients. We projected that enalapril plus folic acid treatment will have a modest lifetime stroke-free survival gain compared with enalapril alone in overall sample, and the benefit will be greater in some specific subgroups. From population health perspective, even a moderate gain may translate into a gain of millions of stroke-free months and will provide critically needed evidence to facilitate clinicians, patients, and policy holders to make informed decisions on stroke prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding

The study was supported by funding from the following: the National Natural Science Foundation of China (grant number 71704064), the Natural Science Foundation of Guangdong Province, China (grant number 2017A030310174), the National Key Research and Development Program (2016YFC0903103), the Presidential Foundation of Nanfang Hospital, Southern Medical University (grant number 2017C007); the Outstanding Youths Development Scheme of Nanfang Hospital, Southern Medical University (2017J009); Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health (grant number U54-GM104941 United States).

Disclosures

T. Zhang reports grants from the National Natural Science Foundation of China (grant number 71704064) and the Natural Science Foundation of Guangdong Province, China (grant number 2017A030310174). Y. Huo reports grants from the National Key Research and Development Program (2016YFC0903103). X. Qin reports grants from the Presidential Foundation of Nanfang Hospital, Southern Medical University (grant number 2017C007) and the Outstanding Youths Development Scheme of Nanfang Hospital, Southern Medical University (2017J009). Z. Zhang reports grants from Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health (grant number U54-GM104941 United States). The other authors report no conflicts.

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Novelty and Significance

What Is New?

- The CSPPT (China Stroke Primary Prevention Trial) demonstrated a significant risk reduction of first stroke in hypertensive patients treated with enalapril plus folic acid compared with those with enalapril alone, but the life time stroke-free survival associated with the treatment is unknown. By establishing adjusted models for competing risks and an age-based time scale using data from 19053 participants of the CSPPT, we estimated lifetime incremental stroke-free survival for enalapril-folic acid versus enalapril alone.

What Is Relevant?

- Compared with enalapril alone, the enalapril plus folic acid treatment projected a mean lifetime stroke-free survival gain of 1.75 months, with an interquartile range from 0.73 to 2.39 months and the maximum gain up to 12.95 months. From population health perspective, even a moderate gain may translate into a gain of millions of stroke-free months and will provide critically needed evidence to facilitate clinicians, patients, and policy holders to make informed decisions on stroke prevention.

Summary

Generally, besides significant benefit in certain subgroups, Enalapril plus folic acid treatment for hypertensive patients is associated with a modest gain in lifetime stroke-free survival, compared with enalapril alone.

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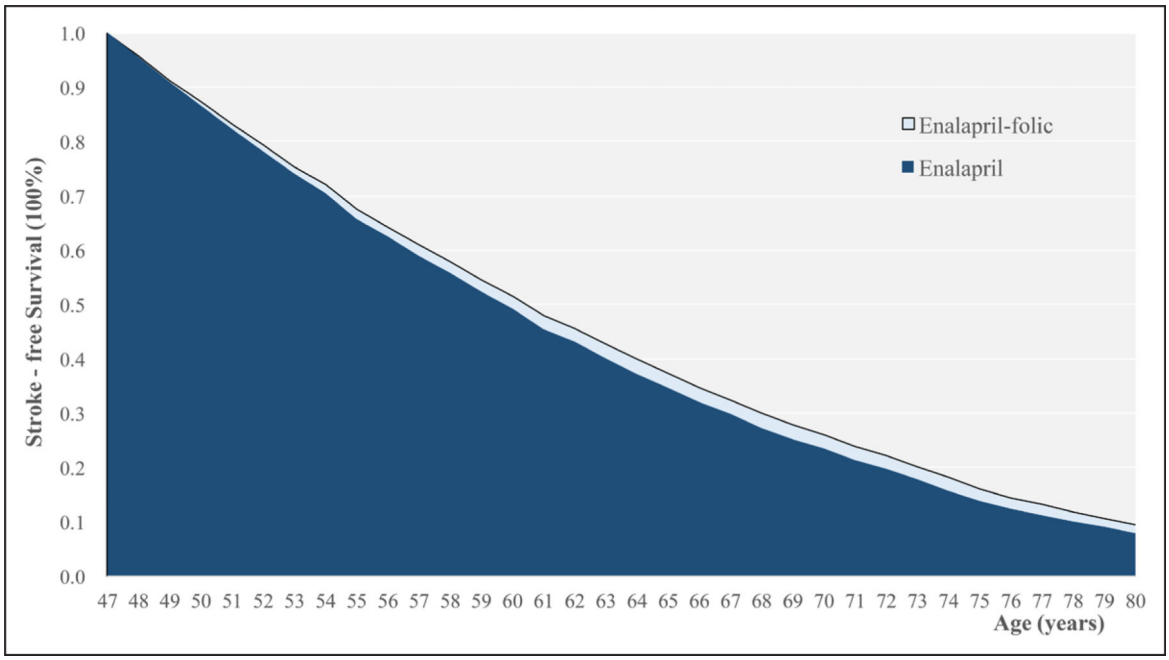

Figure 1.

Predicted folic acid treatment effect for sampled patient. Cumulative survival free of stroke and nonstroke death for 47-year–old male with diabetes mellitus (with fasting blood glucose level of 7.86 mmol/L), total cholesterol level of 8.14 mmol/L, folate level of 2.74 ng/mL, and systolic blood pressure of 185 mm Hg. The effect of enalapril-folic acid is represented by the size of the light blue area between the curves, equal to 7.92 mo.

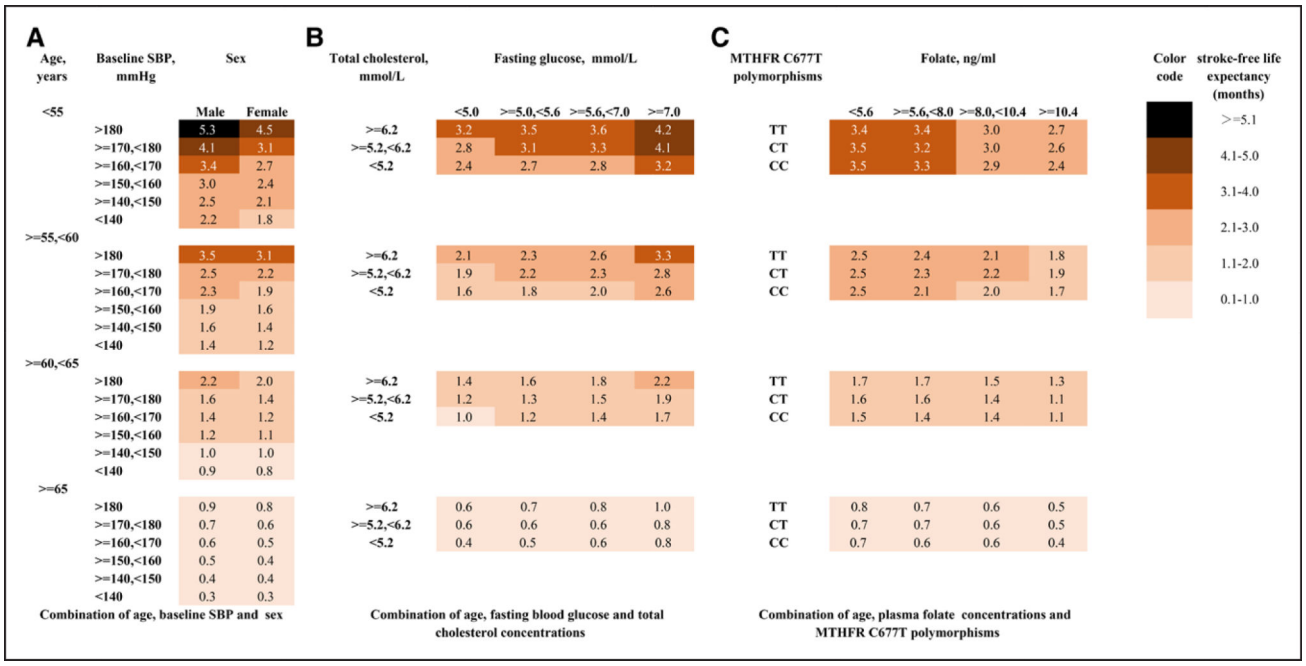

Figure 2.

Predicted lifetime gain in stroke-free survival from enalapril-folic acid compared with enalapril treatment alone. A zero means no treatment effect. A 3.0 means that lifetime enalapril-folic acid treatment is expected to prolong the patient's stroke-free survival by 3 months compared with enalapril alone. **A**, The lifetime stroke-free survival of enalapril-folic acid treatment is higher for younger male individuals with higher systolic blood pressure. **B**, The lifetime benefits of enalapril-folic acid treatment are higher for younger individuals with higher fasting blood glucose and higher total cholesterol. **C**, Younger individuals with lower folate levels and the CT/TT genotype gain more in stroke-free survival. CC indicates MTHFR C677T CC genotype; CT, MTHFR C677T CT genotype; CT, MTHFR C677T CT genotype; MTHFR, methylenetetrahydrofolate reductase; and SBP, systolic blood pressure.

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Table 1.

Baseline Characteristics of Participants in the Final Analysis

Characteristics	Total	Treatment Group		*P* Value
		Enalapril	Enalapril-Folic Acid	
No. (%) with data	**19053**	**9507**	**9546**	
Age, mean (SD), y	60.8 (7.0)	60.8 (7.0)	60.8 (6.9)	0.870
Male, No. (%)	7829 (41.1)	3919 (41.2)	3910 (41.0)	0.713
Body mass index, mean (SD), kg/m^2	24.9 (3.7)	24.8 (3.7)	24.9 (3.7)	0.254
Smoking status, No. (%)				0.242
Never	1 3061 (68.6)	6504 (68.4)	6557 (68.7)	
Former	1478 (7.8)	768 (8.1)	710 (7.4)	
Current	4514 (23.7)	2235 (23.5)	2279 (23.9)	
Alcohol consumption, No. (%)				0.5400
Never	1 3128 (68.9)	6519 (68.6)	6609 (69.2)	
Former	1354 (7.1)	691 (7.3)	663 (6.9)	
Current	4571 (24.0)	2297 (24.2)	2274 (23.8)	
MTHFR C677T polymorphism, No. (%)				0.947
CC genotype	5221 (27.4)	2611 (27.5)	2610 (27.3)	
CT genotype	9348 (49.1)	4653 (48.9)	4695 (49.2)	
TT genotype	4484 (23.5)	2243 (23.6)	2241 (23.5)	
Blood pressure, mean (SD), mm Hg				
Baseline SBP	167.2 (20.4)	167.3 (20.4)	167.1(20.3)	0.504
Baseline DBP	93.7 (11.8)	93.6 (11.9)	93.7 (11.7)	0.429
Mean SBP during treatment period	139.4 (10.8)	139.5 (10.9)	139.3 (10.7)	0.239
Mean DBP during treatment period	82.6 (7.2)	82.6 (7.3)	82.6 (7.2)	0.873
Laboratory results				
TC, mean (SD), mmol/L	5.5 (1.2)	5.5 (1.2)	5.5 (1.2)	0.828
HDL-C, mean (SD), mmol/L	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)	0.677
TG, mean (SD), mmol/L	1.7 (1.2)	1.7 (0.9)	1.7 (1.3)	0.937
Fasting glucose, mean (SD), mmol/L	5.8 (1.7)	5.8 (1.7)	5.8 (1.7)	0.276

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Characteristics	Total	Treatment Group		*P* Value
		Enalapril	Enalapril-Folic Acid	
No. (%) with data	**19053**	**9507**	**9546**	
Creatinine, mean (SD), μmol/L	66.2 (19.5)	66.1 (19.2)	66.2 (19.7)	0.977
Homocysteine, mean (SD), μmol/L	14.5 (8.3)	14.6 (8.5)	14.5 (8.1)	0.394
Folate, mean (SD), ng/mL	8.6 (3.9)	8.6 (3.9)	8.6 (3.9)	0.676
Vitamin B12, mean (SD), pg/mL	412.1 (155.7)	414.5 (161.5)	409.8 (149.6)	0.035

DBP indicates diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; MTHFR, methylenetetrahydrofolate reductase; SBP, systolic blood pressure; TC, total cholesterol; and TG, triglycerides.

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Table 2.

Estimates of β-Coefficients of Projection Models for First Stroke-Risk and Nonstroke Death

Variables	First Stroke		Nonstroke Death	
	β-Coefficients*	*P* Value	β Coefficients*	*P* Value
Treatment (enalapril-folic acid vs enalapril alone)	−0.2439681	0.003	0.0082278	0.924
Study center	0.0465075	0.700	−0.2311645	0.050
Sex (male vs female)	−0.1251136	0.340	−0.2258367	0.084
Mean SBP during treatment period	0.0069797	0.166	0.0290951	<0.001
Mean DBP during treatment period	0.0324575	0.001	0.0157805	0.172
Smoking status	0.1598237	0.010	0.0820128	0.210
Alcohol drinking status	−0.0669677	0.287	0.0155645	0.792
Baseline SBP	0.0136038	<0.001	−0.0051769	0.087
Baseline DBP	0.000034	0.995	−0.0008798	0.884
BMI	0.009459	0.478	−0.0630977	<0.001
TG	−0.1033082	0.071	0.0357859	0.004
HDL-C	−0.1843994	0.187	0.221062	0.117
MTHFR C677T polymorphism	0.0119565	0.848	0.0206116	0.750
Folate	−0.0246603	0.073	−0.0141871	0.267
Vitamin B12	−0.0001864	0.516	0.0004509	0.083
Homocysteine	0.0032583	0.469	0.0108034	0.003
Creatinine	−0.0027568	0.216	0.0059708	<0.001
TC	0.1169953	0.002	−0.0870128	0.040
Fasting glucose	0.1021834	<0.001	0.1036063	<0.001

BMI indicates body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; MTHFR, methylenetetrahydrofolate reductase; SBP, systolic blood pressure; TC, total cholesterol; and TG, triglycerides.

*All analyses were adjusted for age, sex (female, male [reference]), MTHFR C677T genotype (TT, CT, CC [reference]), baseline SBP and DBP, mean SBP and DBP during treatment, BMI, treatment group, study center (Lianyungang, Anqing [reference]), baseline serum folate, vitamin B12, fasting glucose, total cholesterol, triglycerides, HDL-C, homocysteine, creatinine levels, smoking status (current, ever, never [reference]) and alcohol drinking status (current, ever, never [reference]), and the categorical variables are treated as continuous variables.

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Table 3.

Comparison of the Characteristics of Patients With Different Predicted Folic Acid Treatment Effect

Characteristics	Incremental Stroke-Free Survival, Mo				*P* Value
	Q1 (<0.73)	Q2 (≥0.73, <1.42)	Q3 (≥1.42, <2.39)	Q4 (≥2.39)	
No. (%) with data	4763	4763	4763	4764	
Age, mean (SD), y	68.9 (4.0)	62.2 (4.6)	57.7 (4.5)	54.4 (4.3)	<0.001
BMI, mean (SD), kg/m^2	23.4 (3.5)	24.4 (3.5)	25.4 (3.5)	26.3 (3.6)	<0.001
Current smoking (male), No. (%)	1066 (49.1)	969 (51.2)	909 (51.4)	1189 (59.6)	<0.001
Current alcohol drinking (male), No. (%)	1038 (47.8)	984 (52.0)	950 (53.7)	1137 (57.0)	<0.001
MTHFRC677T polymorphisms, No. (%)					<0.001
CC genotype	1477 (31.0)	1383 (29.0)	1253 (26.3)	1108 (23.3)	
CT genotype	2289 (48.1)	2335 (49.0)	2325 (48.8)	2399 (50.4)	
TT genotype	997 (20.9)	1045 (21.9)	1185 (24.9)	1257 (26.4)	
BP, mean (SD), mm Hg					
Baseline SBP	164.0 (18.9)	164.1 (19.6)	165.1 (18.7)	175.7 (21.8)	<0.001
Baseline DBP	86.9 (10.9)	91.1 (10.0)	94.9 (9.8)	101.8 (11.1)	<0.001
Laboratory results (baseline)					
TC, mean (SD), mmol/L	5.3 (1.1)	5.4 (1.2)	5.6 (1.1)	5.9 (1.3)	<0.001
Fasting glucose, mean (SD), mmol/L	5.5 (1.3)	5.6 (1.5)	5.8 (1.5)	6.3 (2.3)	<0.001
Folate, mean (SD), ng/mL	9.3 (4.7)	9.0 (4.0)	8.3 (3.5)	7.8 (3.1)	<0.001

BMI indicates body mass index; BP, blood pressure; DBP, diastolic blood pressure; MTHFR, methylenetetrahydrofolate reductase; SBP, systolic blood pressure; TC, total cholesterol; and TG, triglycerides.