

## Supplementary Online Content

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**eTable 1.** Baseline Characteristics of the CSPPT Participants, Stratified by MTHFR Genotypes and Treatment Groups

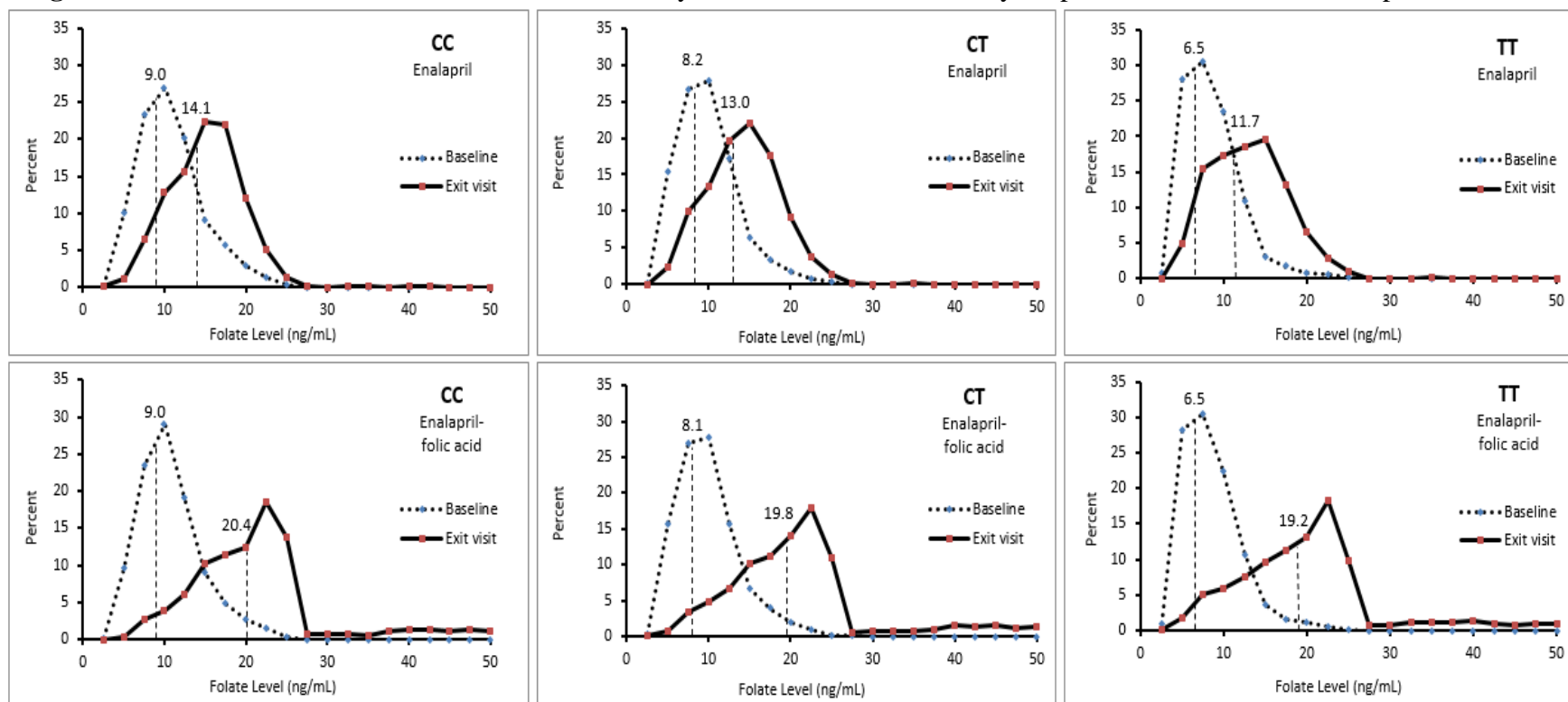
**eTable 2.** Estimates of Crude and Adjusted Hazard Ratios for First Stroke, Stratified by Subgroups Defined by MTHFR Genotypes and Baseline Folate Quartiles Within Each of the Genotypes

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This supplementary material has been provided by the authors to give readers additional information about their work.

**e Figure 1.** Baseline and Exit Serum Folate Distribution by MTHFR C677T Gene Polymorphisms and Treatment Groups



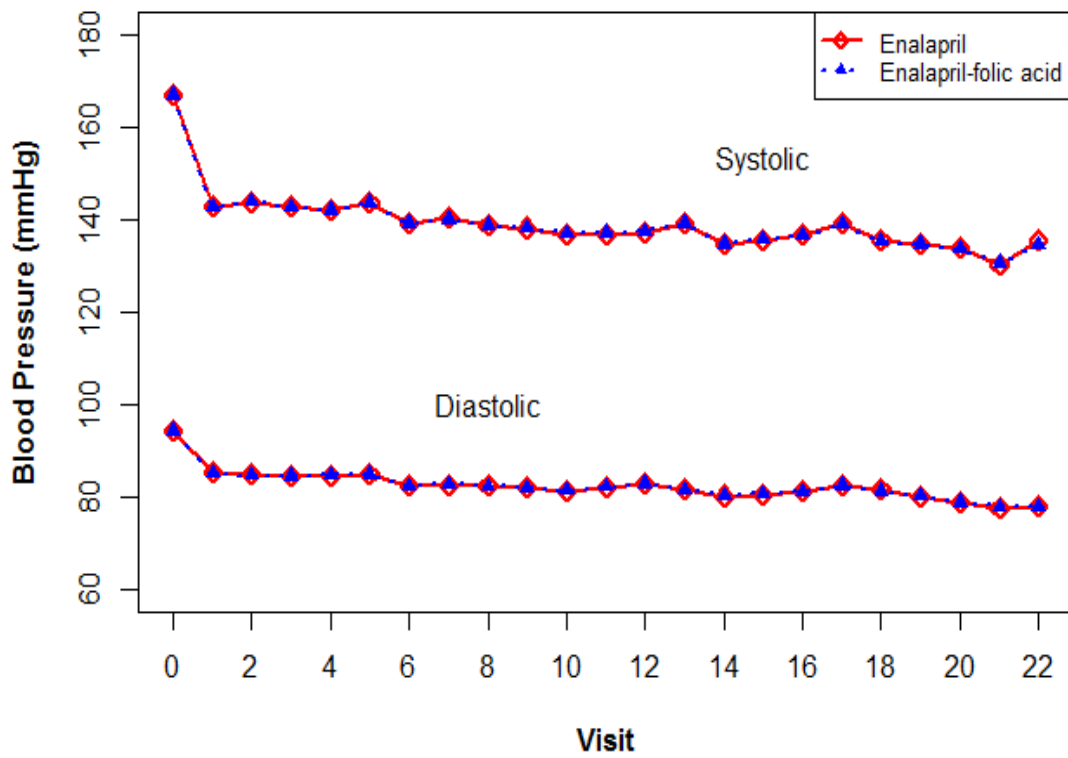
Numbers on the top of the distribution curves and the dashed vertical lines indicate the median folate levels (ng/mL)

The median (25<sup>th</sup>-75<sup>th</sup>) [numbers of individuals] of the baseline and exit folate levels for each genotype:

Folate—ng/mL <sup>&amp;</sup>	CC			CT			TT		
	Enalapril	Enalapril-folic acid	<i>P</i> value	Enalapril	Enalapril-folic acid	<i>P</i> value	Enalapril	Enalapril-folic acid	<i>P</i> value
Baseline	9.0(6.6-11.6) [2810]	9.0(6.5-11.5) [2791]	0.730	8.2(5.7-10.5) [5027]	8.1(5.7-10.5) [5043]	0.568	6.5(4.8-9.1) [2419]	6.5(4.8-9.1) [2409]	0.822
Exit visit	14.1(10.7-16.8) [2260]	20.4(15.4-23.6) [2291]	<0.001	13.0(9.9-16.0) [4138]	19.8(14.7-23.4) [4140]	<0.001	11.7(8.1-14.9) [2020]	19.2(13.8-22.9) [1995]	<0.001

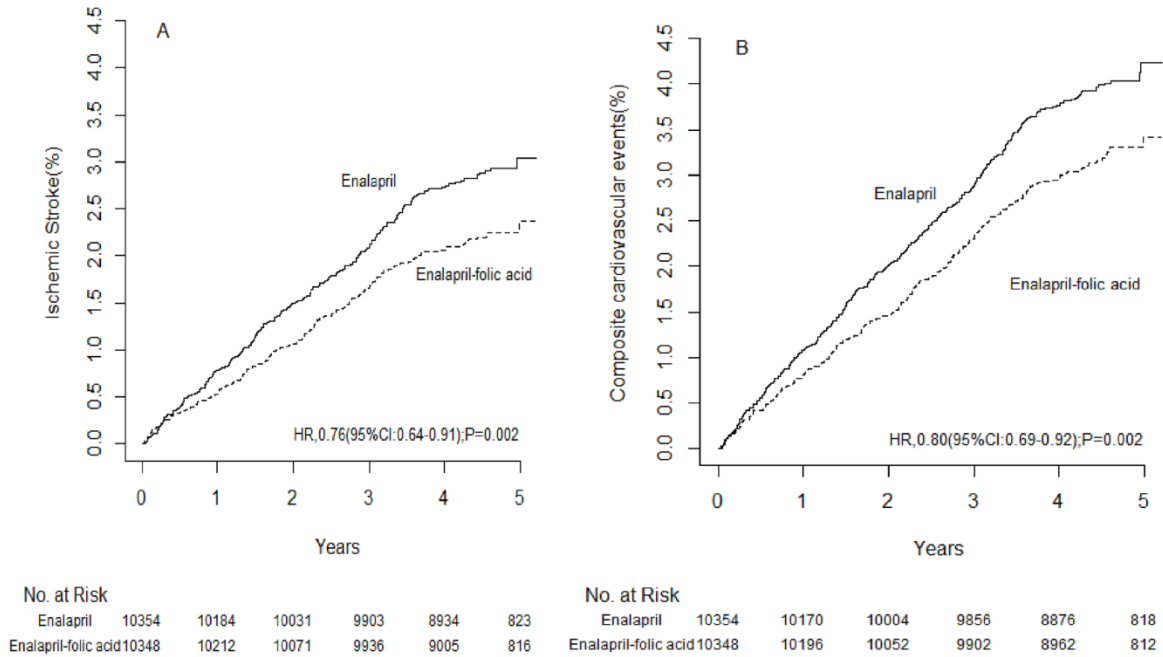
<sup>&</sup>Values are medians (25<sup>th</sup>-75<sup>th</sup>) [number of participants with available data].

**eFigure 2.** Systolic and Diastolic Blood Pressure at the Baseline and Over the Trial Period by Treatment Groups

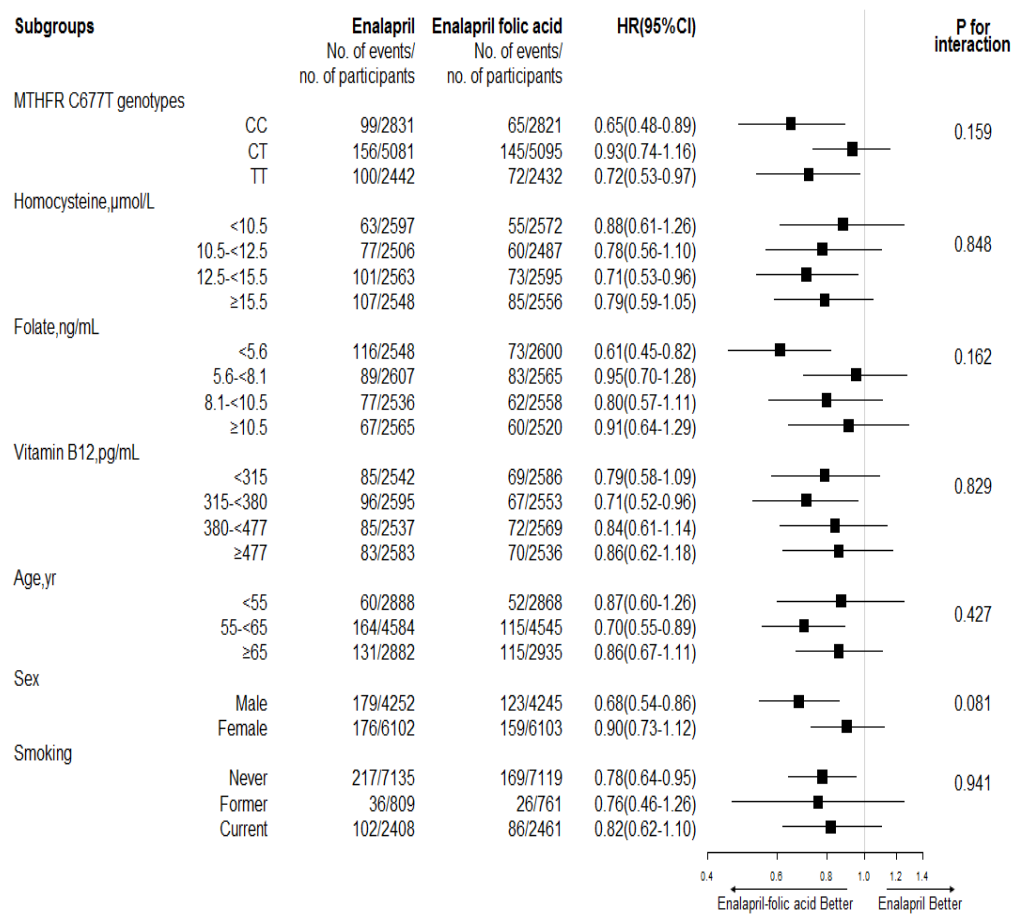


The first visit was at the completion of a 3-week run-in treatment. The subsequent visits during the randomized treatment period were scheduled every 3 months.

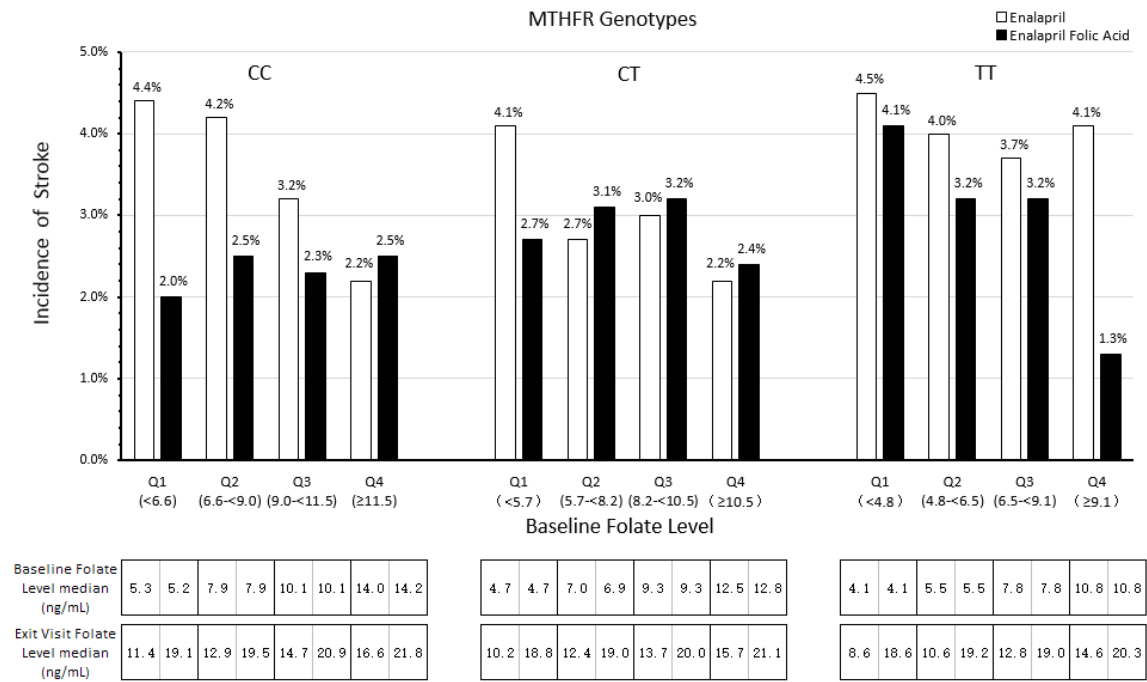
**eFigure 3.** Kaplan-Meier Curves of Cumulative Hazards for (A) Ischemic stroke; (B) Composite Cardiovascular Events



**eFigure 4. Hazard Ratios for First Stroke in Pre-specified Subgroups**



**eFigure 5.** Rates of First Stroke by Treatment Groups, MTHFR Genotypes, and Baseline Folate Levels



Q1, Q2, Q3, Q4 and the number in ( ) represent the quartiles and range of baseline folate levels in specific MTHFR genotype groups.

**eTable 1.** Baseline Characteristics of the CSPPT Participants, Stratified by MTHFR Genotypes and Treatment Groups\*

	CC			CT			TT		
	Enalapril	Enalapril-folic acid	<i>P</i>	Enalapril	Enalapril-folic acid	<i>P</i>	Enalapril	Enalapril-folic acid	<i>P</i>
N	2831	2821		5081	5095		2442	2432	
Male, no. (%)	1187(41.9)	1172(41.6)	0.77	2073(40.8)	2058(40.4)	0.68	992(40.6)	1015(41.7)	0.43
Age—yr	60.1±7.6	60.1±7.5	0.69	59.8±7.6	60.1±7.5	0.07	60.0±7.5	59.8±7.5	0.34
Body-mass index—kg/m <sup>2</sup>	24.6±3.7	24.7±3.7	0.19	25.0±3.7	25.0±3.7	0.60	25.2±3.6	25.1±3.6	0.49
<b>Cardiovascular risk factors—no. (%)</b>									
Smoking			0.65			0.17			0.60
Never	1959(69.2)	1939(68.8)		3474(68.4)	3513(69.0)		1702(69.7)	1667(68.5)	
Former	222(7.8)	208(7.4)		409(8.1)	360(7.1)		178(7.3)	193(7.9)	
Current	650(23.0)	671(23.8)		1196(23.5)	1218(23.9)		562(23.0)	572(23.5)	
Alcohol drinking			0.71			0.57			0.93
Never	1922(67.9)	1929(68.5)		3481(68.5)	3537(69.5)		1710(70.1)	1692(69.6)	
Former	214(7.6)	197(7.0)		370(7.3)	355(7.0)		160(6.6)	163(6.7)	
Current	694(24.5)	691(24.5)		1229(24.2)	1198(23.5)		571(23.4)	577(23.7)	
Hyperlipidemia	78(2.8)	73(2.6)	0.70	141(2.8)	144(2.8)	0.88	59(2.4)	67(2.8)	0.46
Diabetes	78(2.8)	69(2.6)	0.47	150(3.0)	161(3.2)	0.54	107(4.4)	87(3.6)	0.15

**eTable 1.** Baseline Characteristics of the CSPPT Participants, Stratified by MTHFR Genotypes and Treatment Groups (continued)\*

<b>Laboratory results—mmol/L</b>									
Total cholesterol, mg/dL	210.2±43.7	210.2±44.8	1.00	213.3±45.9	214.7±46.6	0.12	216.4±47.5	215.1±46.1	0.31
Triglycerides, mg/dL	146.7±84.5	146.4±180.5	0.95	145.4±79.9	148.1±86.8	0.11	150.3±83.3	147.0±87.0	0.18
HDL cholesterol, mg/dL	52.1±13.9	52.4±13.6	0.36	52.0±13.9	51.9±14.2	0.85	51.3±14.0	51.9±14.1	0.11
Fasting glucose, mmol/L	5.7±1.6	5.6±1.6	0.16	5.8±1.7	5.8±1.7	0.87	6.0±1.9	5.9±1.8	0.25
Creatinine, mg/dL	0.7±0.2	0.7±0.2	0.63	0.7±0.2	0.7±0.2	0.69	0.7±0.2	0.8±0.3	0.06
Homocysteine, μmol/L <sup>#</sup>	11.8 (10.1, 14.2)	11.8 (9.9, 14.0)	0.32	12.1 (10.3, 14.6)	12.2 (10.4, 14.7)	0.10	15.3 (11.9, 21.9)	15.1 (11.7, 21.4)	0.45
Vitamin B12, pg/mL <sup>#</sup>	389.9 (321.8, 489.0)	387.3 (318.3, 492.1)	0.23	382.8 (317.7, 481.4)	383.2 (318.3, 478.3)	0.68	362.6 (305.0, 454.3)	361.6 (304.4-450.3)	0.80
<b>Medication use—no. (%)</b>									
Anti-hypertensive drugs	1236(43.7)	1245(44.1)	0.72	2407(47.4)	2355(46.2)	0.25	1172(48.0)	1121(46.1)	0.18
ACE inhibitors	258(9.1)	283(10.0)	0.24	466(9.2)	451(8.9)	0.57	231(9.5)	204(8.4)	0.19
Angiotensin II–receptor blockers	1(0.04)	1(0.04)	1.00	6(0.12)	5(0.10)	0.76	1(0.04)	4(0.16)	0.18
Calcium channel blockers	316(11.2)	305(10.8)	0.67	490(9.6)	516(10.1)	0.41	229(9.4)	213(8.8)	0.45
Diuretics	56(2.0)	49(1.7)	0.50	118(2.3)	107(2.1)	0.45	43(1.8)	62(2.6)	0.06
β-Blockers	28(1.0)	22(0.8)	0.40	45(0.9)	37(0.7)	0.37	18(0.7)	25(1.0)	0.28
Lipid-lowering drugs	25(0.9)	17(0.6)	0.22	41(0.8)	47(0.9)	0.53	19(0.8)	17(0.7)	0.75
Glucose-lowering drugs	40(1.4)	36(1.3)	0.66	69(1.4)	85(1.7)	0.20	42(1.7)	45(1.9)	0.73
Antiplatelet drugs	66(2.3)	70(2.5)	0.71	177(3.5)	147(2.9)	0.09	79(3.2)	68(2.8)	0.37

\*For continuous variables, values are presented as mean ±SD; <sup>#</sup>Values are medians (25th, 75th percentile), Wilcoxon signed rank test was used.

Abbreviation: ACE, angiotensin-converting enzyme; MTHFR, methylenetetrahydrofolate reductase.



**eTable 2.** Estimates of Crude and Adjusted Hazard Ratios for First Stroke, Stratified by Subgroups Defined by MTHFR Genotypes and Baseline Folate Quartiles Within Each of the Genotypes\*

Folate, ng/mL	No. of events/No. of participants (%)		Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)*	P* value	P* for interaction
	Enalapril (N=10,354)	Enalapril-folic acid (N=10348)				
<b>CC</b>						
≥11.5	16/713(2.2)	17/685(2.5)	1.11(0.56-2.20)	0.98(0.48-2.01)	0.97	Ref
9.0-<11.5	23/711(3.2)	16/712(2.3)	0.69(0.36-1.30)	0.73(0.38-1.41)	0.35	0.506
<9.0	60/1386(4.3)	31/1394(2.2)	0.51(0.33-0.78)	0.45(0.29-0.72)	0.001	0.044
6.6-<9.0	28/665(4.2)	17/689(2.5)	0.58 (0.32-1.07)	0.54(0.29-1.03)	0.06	
<6.6	32/721(4.4)	14/705(2.0)	0.44 (0.23-0.82)	0.37(0.19-0.73)	0.004	
<b>CT</b>						
≥5.7	100/3791(2.6)	109/3777(2.9)	1.10(0.84-1.44)	1.12(0.85-1.49)	0.42	Ref
5.7-<8.2	34/1277(2.7)	40/1293(3.1)	1.17(0.74-1.85)	1.25(0.78-2.01)	0.36	
8.2-<10.5	38/1252(3.0)	39/1235(3.2)	1.04(0.66-1.63)	1.09(0.68-1.74)	0.71	
≥10.5	28/1262(2.2)	30/1249(2.4)	1.08(0.65-1.81)	0.99(0.58-1.70)	0.98	
<5.7	51/1236(4.1)	34/1266(2.7)	0.65(0.42-1.00)	0.69(0.44-1.07)	0.10	0.083
<b>TT</b>						
≥9.1	25/604(4.1)	8/609(1.3)	0.31(0.14-0.70)	0.24(0.10-0.58)	0.001	Ref
4.8-<9.1	47/1217(3.9)	38/1196(3.2)	0.82(0.53-1.25)	0.79(0.51-1.24)	0.31	0.033
4.8-<6.5	25/620(4.0)	19/599(3.2)	0.78(0.43-1.41)	0.74(0.40-1.39)	0.36	
6.5-<9.1	22/597(3.7)	19/597(3.2)	0.86(0.47-1.59)	0.75(0.39-1.43)	0.38	
<4.8	27/598(4.5)	25/604(4.1)	0.92(0.53-1.58)	0.96(0.55-1.66)	0.88	0.011

\* Adjusted for age, sex, SBP and DBP at baseline, mean SBP and DBP during treatment period, body-mass index, study centers, baseline homocysteine, vitamin B12, creatinine, total cholesterol, triglycerides, HDL cholesterol, fasting glucose levels, smoking, and alcohol consumption;

Baseline folate quartiles within each of the genotype -CC: <6.6, 6.6-<9.0, 9.0-<11.5, ≥11.5; CT: <5.7, 5.7-<8.2, 8.2-<10.5, ≥10.5; TT: <4.8, 4.8-<6.5, 6.5-<9.1, ≥9.1.

**eTable 3.** Adverse Events by the Medical Dictionary for Regulatory Activities Primary System Organ Classification (SOC) (Safety Set)

SOC	Enalapril (N=10,119)		Enalapril-folic acid (N=10,124)		<i>P</i> Value*
	Frequency <sup>&amp;</sup>	Participant, No. (%)	Frequency <sup>&amp;</sup>	Participant, No. (%)	
Respiratory, thoracic and mediastinal disorders	17734	5470(54.1)	17378	5447(53.8)	0.85
Nervous system disorders	1517	1204(11.9)	1524	1243(12.2)	0.48
Gastrointestinal disorders	703	579(5.7)	749	610(6.0)	0.40
General disorders and administration site conditions	448	403(4.0)	437	401(4.0)	0.97
Injury, poisoning and procedural complications	390	350(3.5)	409	358(3.5)	0.80
Cardiac disorders	274	217(2.1)	238	199(2.0)	0.41
Infections and infestations	232	216(2.1)	229	214(2.1)	0.96
Musculoskeletal and connective tissue disorders	221	209(2.1)	225	191(1.9)	0.40
Eye disorders	177	169(1.7)	186	171(1.7)	0.96
Unclassified	108	104(1.0)	122	116(1.1)	0.46
Hepatobiliary disorders	100	91(0.9)	126	116(1.1)	0.10
Neoplasms benign, malignant and unspecified	88	79(0.8)	88	82(0.8)	0.88
Vascular disorders	80	78(0.8)	82	78(0.8)	1.00
Renal and urinary disorders	69	61(0.6)	87	78(0.8)	0.18
Endocrine disorders	57	52(0.5)	59	56(0.6)	0.78
Reproductive system and breast disorders	47	43(0.4)	40	37(0.4)	0.58

**eTable 3.** Adverse Events by the Medical Dictionary for Regulatory Activities Primary System Organ Classification (SOC) (Safety Set) (continued)

Skin and subcutaneous tissue disorders	39	37(0.4)	29	28(0.3)	0.32
Surgical and medical procedures	24	24(0.2)	22	19(0.2)	0.54
Metabolism and nutrition disorders	20	19(0.2)	23	23(0.2)	0.65
Ear and labyrinth disorders	18	18(0.2)	18	16(0.2)	0.86
Immune system disorders	18	16(0.2)	19	18(0.2)	0.87
Blood and lymphatic system disorders	16	15(0.1)	14	14(0.1)	1.00
Psychiatric disorders	6	6(0.06)	13	12(0.1)	0.24

&The Frequency columns present the number of events;

\*Comparisons for the percentages of participants between groups.

**eTable 4. Drug Related Adverse Events (Safety Set)**

Adverse events	Enalapril (N=10,119)		Enalapril-folic acid (N=10,124)		P Value*
	Frequency <sup>&amp;</sup>	Participant, No. (%) <sup>#</sup>	Frequency <sup>&amp;</sup>	Participant, No.(% ) <sup>#</sup>	
Cough	2852	2011(19.9)	2851	2009(19.8)	0.98
Headache	57	56(0.6)	44	44(0.4)	0.27
Abdominal discomfort	19	19(0.2)	25	25(0.2)	0.45
Nausea	9	9	9	9	1.00
Flushing	4	4	8	8	0.39
Oropharyngeal discomfort	6	6	6	6	1.00
Chest discomfort	5	5	4	4	1.00
Palpitations	3	3	5	5	0.72
Diarrhea	6	6	2	2	0.29

<sup>&</sup>The Frequency columns present the number of events;

<sup>#</sup> Only the events with percentages more than 0.1% are presented;

\* Comparisons for the percentages of participants between groups.