

**Supplemental Table 1. Baseline characteristics of the CSPPT study participants\***

	Total		Enalapril		Enalapril-folic acid	
	Excluded	Included	Excluded	Included	Excluded	Included
N	3835	16867	1905	8449	1930	8418
Male, no. (%)	1703 (44.4)	6794 (40.3)	844 (44.3)	3408 (40.3)	859 (44.5)	3386 (40.2)
Age—yr	59.8 ± 8.1	60.0 ± 7.4	59.8 ± 8.1	60.0 ± 7.4	59.9 ± 8.1	60.1 ± 7.4
Body-mass index—kg/m <sup>2</sup>	24.5 ± 3.7	25.1 ± 3.7	24.5 ± 3.7	25.0 ± 3.7	24.5 ± 3.7	25.1 ± 3.7
MTHFR C677T polymorphisms—no. (%)						
CC	1092 (28.5)	4560 (27.0)	556 (29.2)	2275 (26.9)	536 (27.8)	2285 (27.1)
CT	1897 (49.5)	8279 (49.1)	933 (49.0)	4148 (49.1)	964 (49.9)	4131 (49.1)
TT	846 (22.1)	4028 (23.9)	416 (21.8)	2026 (24.0)	430 (22.3)	2002 (23.8)
<b>Cardiovascular risk factors—no. (%)</b>						
Smoking						
Never	2529(66.0)	11725(69.5)	1260(66.2)	5875(69.5)	1269(65.8)	5850(69.6)
Former	297 (7.7)	1273 (7.6)	154 (8.1)	655 (7.8)	143 (7.4)	618 (7.3)
Current	1007 (26.3)	3862 (22.9)	490 (25.7)	1918 (22.7)	517 (26.8)	1944(23.1)
<b>Laboratory results, mg/dL</b>						
Total cholesterol	211.5 ± 45.6	213.8 ±45.9	210.3 ±44.8	213.8 ± 45.9	212.6 ± 46.4	213.8 ± 46.0
Triglycerides	144.2 ± 86.9	147.8±105.9	143.7 ± 85.2	147.6 ± 81.3	144.7 ± 88.5	148.0 ± 125.8
HDL cholesterol	52.6 ± 14.3	51.8 ± 13.9	52.2 ± 14.2	51.8 ± 13.9	53.0 ± 14.4	51.8 ± 13.9
Fasting glucose	103.5 ± 33.4	104.7 ± 29.9	103.5 ±33.3	105.0 ± 30.5	103.5 ± 33.6	104.4 ± 29.3
Homocysteine, μmol/L	14.6 ± 8.5	14.4± 8.3	14.8 ± 8.8	14.5 ± 8.5	14.5 ± 8.3	14.4 ± 8.1
Vitamin B12, pg/mL	417.2 ± 155.8	411.5 ± 157.3	420.1±160.9	413.6 ± 163.9	414.3 ± 150.6	409.4 ± 150.4
Folate, ng/mL	9.0 ± 4.1	8.5 ± 3.8	9.1 ± 4.2	8.5 ± 3.8	8.9 ± 4.0	8.5 ± 3.9
eGFR, ml/min/1.73m <sup>2</sup>	93.1 ± 14.3	93.6 ± 13.0	93.0 ± 14.6	93.7 ± 12.8	93.2 ± 13.9	93.5 ± 13.1
<b>Medication use—no. (%)</b>						
Anti-hypertensive drugs	1633 (42.6)	7903 (46.9)	835 (43.8)	3980 (47.1)	798 (41.3)	3923 (46.6)
ACE inhibitors	321 (8.4)	1572 (9.3)	172 (9.0)	783 (9.3)	149 (7.7)	789 (9.4)
Ang II type I-receptor blockers	3 (0.1)	15 (0.1)	1 (0.1)	7 (0.1)	2 (0.1)	8 (0.1)
Calcium channel blockers	395 (10.3)	1674 (9.9)	205 (10.8)	830 (9.8)	190 (9.8)	844 (10.0)
Diuretics	73 (1.9)	362 (2.1)	33 (1.7)	184 (2.2)	40 (2.1)	178 (2.1)
β-Blockers	28 (0.7)	147 (0.9)	13 (0.7)	78 (0.9)	15 (0.8)	69(0.8)
Lipid-lowering drugs	24 (0.6)	142 (0.8)	12 (0.6)	73 (0.9)	12 (0.6)	69(0.8)
Glucose-lowering drugs	56 (1.5)	261 (1.5)	34 (1.8)	117 (1.4)	22(1.1)	144 (1.7)

**Abbreviations:** ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; MTHFR, methylenetetrahydrofolate reductase.

\*For continuous variables, values are presented as mean ±SD.

**Supplemental Table 2. Systolic blood pressure levels (mmHg) at baseline and over the treatment period by treatment group \***

	Enalapril	Enalapril-folic acid	<i>P</i> value
<b>All participants</b>			
N	8449	8418	
At baseline	167.3 ± 20.6	167.2 ± 20.4	0.839
Over treatment period	139.2 ± 10.9	139.2 ± 10.7	0.575
<b>Baseline total homocysteine</b>			
<b>&lt;12.5µmol/L (median)</b>			
N	4260	4189	
At baseline	166.5 ± 19.7	166.5 ± 20.0	0.983
Over treatment period	138.6 ± 10.5	138.7 ± 10.6	0.738
<b>≥12.5µmol/L</b>			
N	4189	4229	
At baseline	168.1 ± 21.3	168.0 ± 20.8	0.761
Over treatment period	139.9 ± 11.2	139.7 ± 10.8	0.242

\*Values are presented as mean ± SD.

**Supplemental Table 3. Diastolic blood pressure levels (mmHg) at baseline and over the treatment period by treatment group \***

	Enalapril	Enalapril-folic acid	<i>P</i> value
<b>All participants</b>			
N	8449	8418	
At baseline	94.1 ± 12.1	94.3 ± 11.7	0.344
Over treatment period	82.8 ± 7.4	82.8 ± 7.2	0.959
<b>Baseline total homocysteine</b>			
<b>&lt;12.5µmol/L (median)</b>			
N	4260	4189	
At baseline	93.9 ± 11.6	94.2 ± 11.4	0.405
Over treatment period	82.9 ± 7.3	83.0 ± 7.2	0.458
<b>≥12.5µmol/L</b>			
N	4189	4229	
At baseline	94.3 ± 12.5	94.4 ± 12.1	0.616
Over treatment period	82.6 ± 7.5	82.5 ± 7.3	0.526

\*Values are presented as mean ± SD.

**Supplemental Table 4. Concomitant medication usage during the treatment period by treatment group\***

Medication, No. (%)	Enalapril	Enalapril-Folic Acid	<i>P</i> value*
Anti-hypertension drugs			
Calcium channel blockers	6958 (82.4)	6947 (82.5)	0.768
Diuretics	4451 (52.7)	4447 (52.8)	0.849
Glucose-lowering drugs	143 (1.7)	137 (1.6)	0.741
Lipid-lowering drugs	13 (0.2)	13 (0.2)	0.993
Antiplatelet drugs	69 (0.8)	62 (0.7)	0.553

\*Regular concomitant medication was defined as taking the drug of interest for 180 or more cumulative days;

**Supplemental Table 5. Stratified analyses by the baseline use of ACEIs and the concomitant use of CCBs \* during the trial period for the change in total homocysteine levels†**

	Enalapril	Enalapril-Folic Acid	$\beta$ (95%CI) ‡	<i>P</i> for interaction‡
Baseline use of ACEIs				0.866
Yes	-0.3 (6.7)	-1.6 (6.3)	-1.78 (-2.25, -1.31)	
No	0.2 (7.1)	-1.5 (7.8)	-1.66 (-1.85, -1.47)	
Concomitant use of CCBs during the trial period				0.111
Yes	0.2 (7.2)	-1.5 (7.9)	-1.73 (-1.94, -1.52)	
No	0.0 (6.6)	-1.5 (6.4)	-1.33 (-1.65, -1.00)	

\*Regular concomitant medication was defined as taking the drug of interest for 180 or more cumulative days;

†Values are presented as mean (standard deviation);

‡Adjusted for age, sex, study center, use of angiotensin-converting enzyme inhibitors (ACEIs), *MTHFR* C677T genotypes, smoking status, body mass index (BMI), total homocysteine, fasting glucose, total cholesterol (TC), eGFR, folate, vitamin B12, uric acid and systolic blood pressure (SBP) at baseline, as well as time-averaged SBP, concomitant use of calcium channel blockers (CCBs) and concomitant use of diuretics during the trial period.

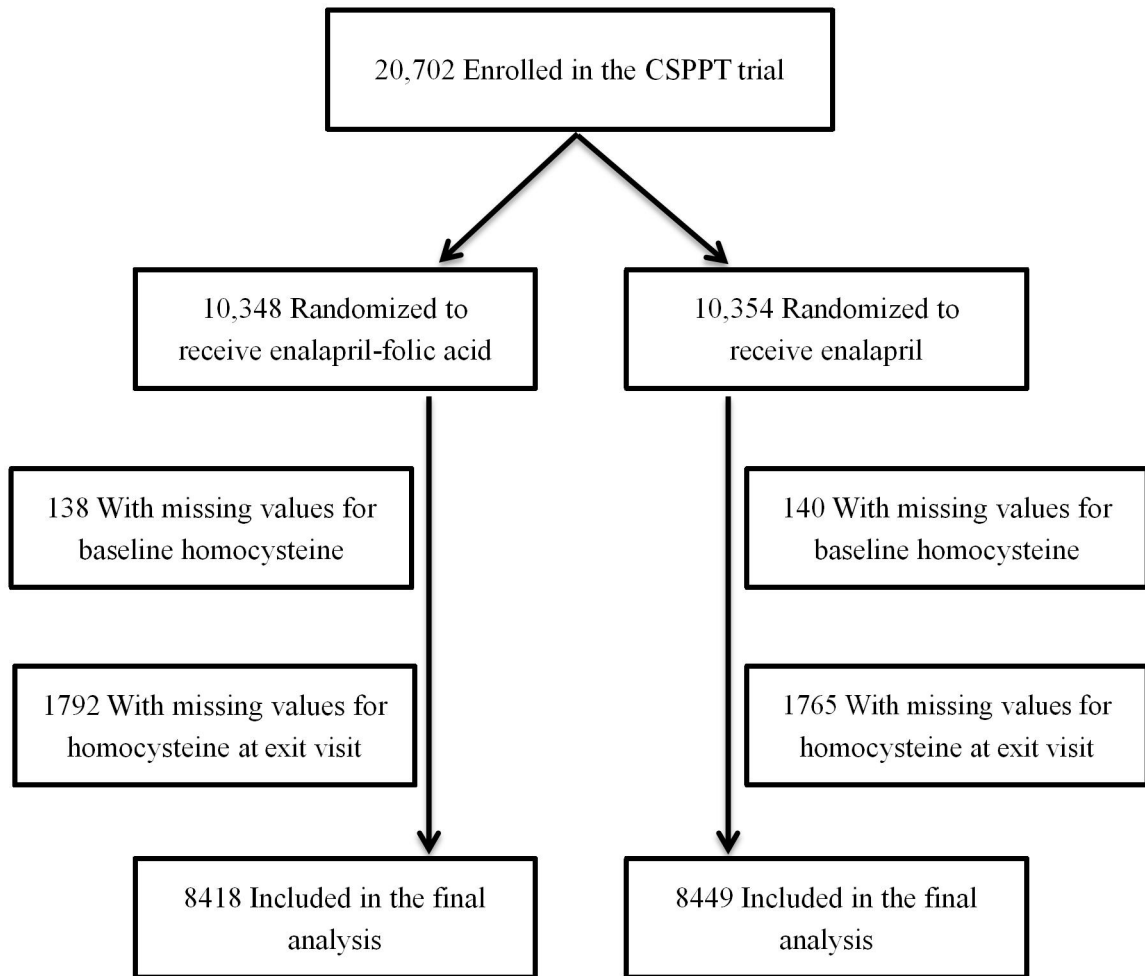
**Supplemental Table 6. Mean total homocysteine levels ( $\mu\text{mol/L}$ ) at baseline and exit visits by treatment group in participants with metabolic B12 deficiency \***

	Enalapril	Enalapril-folic acid	<i>P</i> value
N	334	347	
At baseline	18.6(10.6)	17.7 (6.3)	0.161
At exit	19.8 (17.1)	17.9 (16.3)	0.134
Change <sup>†</sup>	-1.3 (13.5)	-0.3 (13.8)	0.348
Change by group <sup>‡</sup>		-1.0 (-3.0, 1.1)	

\*Values are presented as mean (standard deviation);

<sup>†</sup>Change= total homocysteine level at exit- total homocysteine level at baseline;

<sup>‡</sup> Mean (95%CI).



**Supplemental Figure 1. Flow chart of the participants.**