Impact of Achieved Blood Pressure on First Stroke in Uncomplicated Grade 1 Hypertension

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Background—We aimed to test the impact of achieved blood pressure (BP) on first stroke among patients with grade 1 hypertension and without cardiovascular diseases in the China Stroke Primary Prevention Trial.

Methods and Results—A total of 3187 patients with uncomplicated grade 1 hypertension were included. The risk of outcomes was assessed according to: (1) the proportion of visits in which BP was reduced to <140/90 mm Hg, and (2) the time-averaged systolic BP (SBP) or diastolic BP levels during the study treatment period. The median antihypertensive treatment duration was 4.6 years. Only 1.5% of the participants discontinued the treatments because of adverse reaction. Overall, the risk of stroke decreased with the increase of the proportion of study visits with BP <140/90 mm Hg (for per 5% increase; hazard ratio, 0.92 [95% CI, 0.87–0.98]). Consistently, compared with patients with time-averaged SBP ≥140 or diastolic BP ≥90 mm Hg, the risk of stroke was lower in patients with time-averaged SBP of 120 to <140 mm Hg (1.1% versus 2.9%; hazard ratio, 0.39 [95% CI, 0.22–0.69]) or diastolic BP <90 mm Hg (1.5% versus 2.7%; hazard ratio, 0.41 [95% CI, 0.17–0.98]). The beneficial results were consistent across age (<60 versus ≥60 years), sex, baseline SBP (<150 versus 150 to <160 mm Hg), study treatment groups (enalapril or enalapril-folic acid), and hypertension subtypes (isolated systolic hypertension or systolic-diastolic hypertension). However, a time-averaged SBP <120 mm Hg (versus 120–140 mm Hg) was associated with an increased risk for stroke. Similar results were observed for composite cardiovascular events or all-cause death.

Conclusions—Achieved BP <140/90 mm Hg was significantly associated with a decreased risk of stroke or all-cause death in patients with uncomplicated grade 1 hypertension. (*J Am Heart Assoc*. 2017;6:e005247. DOI: 10.1161/JAHA.116.005247.)

Key Words: achieved blood pressure • all-cause death • cardiovascular disease prevention • grade 1 hypertension • high blood pressure • hypertension • primary prevention • stroke

Hypertension has become a highly important public health challenge, affecting more than 1 billion adults worldwide.[1] More important, most hypertensive patients have grade 1 hypertension (untreated systolic blood pressure [SBP] of 140–159 mm Hg and/or diastolic blood pressure [DBP] of 90–99 mm Hg) and no previous cardiovascular diseases.[2] The decision to treat this population has important clinical (eg, adverse drug effects, lifetime of drug therapy) and public

health (eg, high cost of drugs, medical services) implications.[3] However, whether these patients should be treated remains controversial.

Antihypertensive drugs are recommended for patients with grade 1 hypertension at low to moderate risk after months of unsuccessful lifestyle measures according to the 2013 European Society of Hypertension/European Society of Cardiology guidelines (class IIa, level B),[4] the 2014 American

Society of Hypertension/International Society of Hypertension guidelines,[5] and the 2014 Eighth Joint National Committee report (expert opinion, grade E).[6] However, the 2011 National Institute for Health and Care Excellence[7] guideline recommended antihypertensive treatment only for patients with grade 1 hypertension at high total cardiovascular risk. The 2016 Hypertension Canada's Canadian Hypertension Education Program guidelines[8] also recommended that antihypertensive therapy should be considered for patients with grade 1 hypertension only in those with macrovascular target organ damage or other independent cardiovascular risk factors. The inconsistency in the recommendations among these major guidelines shows that the evidence concerning drug treatment in uncomplicated grade 1 hypertension is scanty and controversial.[4,9]

The China Stroke Primary Prevention Trial (CSPPT) found that the combined use of enalapril and folic acid, compared with enalapril alone, significantly reduced the risk of first stroke by 21% (hazard ratio [HR], 0.79; 95% CI, 0.68–0.93) in Chinese hypertensive patients without a history of cardiovascular diseases.[10] The CSPPT included about half of hypertensive patients without previously antihypertensive treatment and with different on-treatment blood pressure (BP) levels, which offers us an exceptional opportunity to investigate the relationship between achieved BP and cardiovascular outcomes or all-cause death in patients with grade 1 hypertension. Therefore, the current study, a post hoc analysis of the CSPPT, aimed to test the impact of achieved BP on first stroke among patients with grade 1 hypertension and without cardiovascular diseases.

Methods

Study Design

The rationale and study design for the CSPPT have previously been reported in detail.[10] Briefly, the CSPPT was a multicommunity, randomized, double-blind, controlled trial conducted from May 19, 2008, to August 24, 2013, in 32 communities in Jiangsu (20 communities) and Anhui (12 communities) provinces. The CSPPT was approved by the ethics committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number: FWA00001263) and registered with ClinicalTrials.gov (NCT00794885). All participants gave written informed consent. The study enrolled a total of 20 702 hypertensive adults without a history of cardiovascular disease.

Study Population

This study enrolled patients with grade 1 hypertension among the previously untreated hypertensive adults in the CSPPT.

Untreated hypertension in the CSPPT was defined as not receiving antihypertensive medication within the past 2 weeks.

Detailed inclusion and exclusion criteria for the CSPPT are described elsewhere. Eligible participants were men and women aged 45 to 75 years with hypertension, defined as seated resting SBP ≥140 mm Hg or DBP ≥90 mm Hg at both the screening and recruitment visits, or patients who were taking antihypertensive medication. The major exclusion criteria included history of physician-diagnosed stroke, myocardial infarction, heart failure, post-coronary revascularization, and/or congenital heart disease.

Intervention and Follow-Up

Eligible participants were randomly assigned in a 1:1 ratio to 1 of 2 treatment groups: a daily oral dose of 1 tablet containing 10 mg enalapril and 0.8 mg folic acid (single-tablet combination, the enalapril-folic acid group); or a daily oral dose of 1 tablet containing 10 mg enalapril only (the enalapril only group). Other classes of antihypertensive medications, mostly dihydropyridine calcium channel blockers and hydrochlorothiazide, could be prescribed concomitantly if necessary. BP control within a normal range (SBP <140 mm Hg and DBP <90 mm Hg) was not mandatory.

Participants were followed up every 3 months. At each visit, BP and pulse rates of the participants were measured, the number of pills taken between visits were counted, and concomitant medications and adverse events were recorded.

At each visit, seated BP measurements were obtained by trained research staff using a mercury manometer after the patients had been seated for 10 minutes. The standard method and appropriately sized cuffs were used. Triplicate measurements on the same arm were taken, with at least 2 minutes between readings. The mean SBP and DBP values of the 3 independent measures were used in the analysis.

Outcomes

The primary outcome was a first nonfatal or fatal stroke (ischemic or hemorrhagic), excluding subarachnoid hemorrhage and silent stroke. Stroke was defined as rapidly developed clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer (unless interrupted by surgery or death) or a demonstrable lesion on computed tomography or magnetic resonance imaging scan that was consistent with acute stroke, with no apparent causes other than of vascular origin. Computed tomography or magnetic resonance imaging were not essential for diagnosis of stroke, but were necessary for differentiating the subtypes of stroke (ischemic or hemorrhagic). Without imaging data, stroke was still diagnosed in the presence of specific signs and symptoms of focal disturbance

of cerebral function and the subtype defined as "uncertain" (see the protocol the CSPPT[1]).

Secondary outcomes included a composite of cardiovascular events (cardiovascular death, myocardial infarction, and stroke) and all-cause death.

All of the study outcomes were reviewed and adjudicated according to standard criteria by an independent end point adjudication committee.

Statistical Analysis

The current study included a total of 3187 patients with grade 1 hypertension from the CSPPT (Figure 1). There were missing values on serum total cholesterol (n=56), body mass index (n=1), smoking status (n=3), drinking status (n=4), serum folate (n=24), serum homocysteine (n=43), serum vitamin B12 (n=24), serum fasting glucose (n=57), and estimated glomerular filtration rate levels (n=58) at baseline. Multiple imputations, with a number of 5 imputed data sets and an imputation method of predictive mean matching, were used to deal with missing values in the outcome analyses by fitting a model to each of the imputed data sets and then pooling the results together in a "mice" package of R (R software, http://www.R-project.org/).

Time-averaged BP levels during the treatment period were calculated for each participant using all postbaseline results up to the last visit before the date of an event or the end of

follow-up in those without an event (times of BP measurement during the treatment period: median, 16; interquartile range, 12–18 times). Diabetes mellitus was defined as having a history of diabetes mellitus or a fasting glucose ≥7 mmol/L at baseline or under glucose-lowering therapy. Hypertension subtypes were defined as follows: systolic-diastolic hypertension (SBP ≥140 and DBP ≥90 mm Hg), isolated systolic hypertension (SBP ≥140 and DBP <90 mm Hg), or isolated diastolic hypertension (SBP <140 and DBP ≥90 mm Hg). Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Participants were divided into 4 groups according to the proportion of study visits (<25 [reference], 25–<50, 50–<75, and ≥75%) in which BP was reduced to <140/90 mm Hg up to the occurrence of an event or, in those without an event, up to study end. No minimum number of visits was required for patients to be included in the analysis. Furthermore, the participants were divided into groups according to the time-averaged SBP (<120, 120–<140 [reference], and ≥140 mm Hg) or DBP (<75, 75–<80, 80–<90, and ≥90 [reference] mm Hg) levels during the treatment period.

Cox proportional hazards models were used to estimate the HRs and 95% CIs for the risk of study outcomes associated with the proportion (continuous and categorical) of study visits in which BP was <140/90 mm Hg and time-averaged BP levels, without and with adjustment for age, sex,
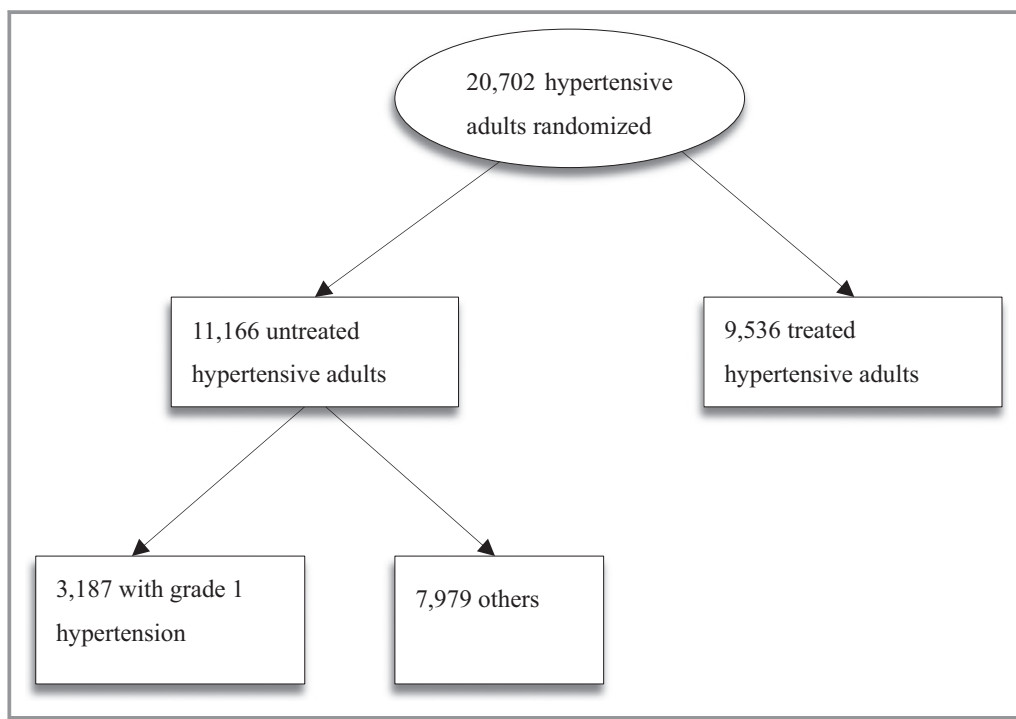

Figure 1. Flow chart of the participants.

Table 1. Characteristics of the Study Participants According to the Proportion of Visits in Which BP was Reduced to <140/90 mm Hg*

	Total (N=3187)	Proportions				P Value
		<25% (n=295)	25% to <50% (n=722)	50% to <75% (n=1257)	≥75% (n=913)	
Age, y	59.4 (7.4)	58.6 (8.3)	59.5 (7.5)	59.7 (7.2)	59.3 (7.1)	0.129
Male, No. (%)	1316 (41.3)	136 (46.1)	305 (42.2)	553 (44.0)	322 (35.3)	<0.001
Body mass index, kg/m^2	24.0 (3.6)	24.2 (3.9)	24.2 (3.6)	24.0 (3.5)	24.0 (3.5)	0.555
Current smoking, No. (%)	816 (25.6)	95 (32.2)	181 (25.1)	354 (28.2)	186 (20.4)	<0.001
Current alcohol drinking, No. (%)	869 (27.3)	99 (33.4)	207 (28.7)	358 (28.5)	205 (22.5)	0.005
MTHFR C677T polymorphisms, No. (%)						
CC	941 (29.5)	89 (30.2)	213 (29.5)	357 (28.4)	282 (30.9)	0.648
CT	1553 (48.7)	144 (48.8)	338 (46.8)	634 (50.4)	437 (47.9)	
TT	693 (21.8)	62 (21.0)	171 (23.7)	266 (21.2)	194 (21.2)	
Treatment group, No. (%)						
Enalapril	1579 (49.6)	144 (48.8)	357 (49.5)	620 (49.3)	458 (50.2)	0.973
Enalapril-folic acid	1608 (50.4)	151 (51.2)	365 (50.5)	637 (50.7)	455 (49.8)	
Baseline BP, mm Hg						
Systolic	150.9 (6.4)	150.8 (6.9)	151.5 (6.4)	151.0 (6.3)	150.1 (6.3)	<0.001
Diastolic	87.6 (7.9)	89.2 (8.0)	88.4 (7.9)	87.4 (8.1)	86.8 (7.5)	<0.001
Time-averaged BP during the treatment period, mm Hg						
Systolic	135.4 (9.6)	151.6 (8.4)	142.0 (6.0)	134.4 (5.0)	126.2 (5.2)	<0.001
Diastolic	81.0 (6.6)	88.5 (7.5)	84.0 (6.1)	80.5 (5.5)	76.9 (4.6)	<0.001
Self-reported hyperlipidemia	59 (1.9)	2 (0.7)	15 (2.1)	26 (2.1)	16 (1.8)	0.421
Self-reported diabetes mellitus	67 (2.1)	6 (2.0)	12 (1.7)	28 (2.2)	21 (2.3)	0.812
Laboratory results						
Fasting glucose, mmol/L	5.6 (1.6)	5.7 (1.8)	5.6 (1.6)	5.6 (1.6)	5.5 (1.4)	0.342
Total cholesterol, mmol/L	5.4 (1.2)	5.2 (1.1)	5.3 (1.1)	5.4 (1.2)	5.5 (1.1)	<0.001
Creatinine, μmol/L	64.4 (15.5)	66.7 (20.4)	64.6 (14.4)	64.4 (14.3)	63.6 (16.2)	0.029
Homocysteine, μmol/L	13.8 (7.2)	14.4 (9.1)	14.2 (8.6)	13.7 (6.7)	13.2 (6.0)	0.027
Folate, ng/mL	9.3 (4.4)	9.2 (4.2)	9.3 (4.2)	9.4 (4.9)	9.2 (4.0)	0.856
Medication use, No. (%)						
Lipid-lowering drugs	7 (0.2)	1 (0.3)	1 (0.1)	4 (0.3)	1 (0.1)	0.689
Glucose-lowering drugs	32 (1.0)	2 (0.7)	7 (1.0)	15 (1.2)	8 (0.9)	0.819
Antiplatelet drugs	10 (0.3)	0 (0)	1 (0.3)	6 (0.5)	3 (0.3)	0.437

BP indicates blood pressure; MTHFR, methylenetetrahydrofolate reductase.
*Values are presented as mean (SD) for continuous variables.

study centers, methylenetetrahydrofolate reductase C677T polymorphism, study treatment groups, body mass index, smoking, alcohol drinking status, SBP, DBP, estimated glomerular filtration rate, fasting glucose, total cholesterol, folate, vitamin B12, and homocysteine levels at baseline.

A 2-tailed P<0.05 was considered statistically significant in all analyses. R software version 3.3.1 was used for all statistical analyses.

Results

Cohort in Analysis and Baseline Characteristics

A total of 3187 participants with grade 1 hypertension at baseline were included in the analyses. The flow of the participants is presented in Figure 1.

Baseline characteristics of the 4 groups of participants according to the proportion of study visits in which BP

Table 2. Characteristics of the Study Participants by Time-Averaged SBP Levels* During the Treatment Period

	Time-Averaged SBP, mm Hg			
	≥140 (n=870)	120 to <140 (n=2215)	<120 (n=102)	P Value
Age, y	60.2 (7.6)	59.2 (7.2)	57.8 (7.3)	<0.001
Male, No. (%)	374 (43.0)	916 (41.4)	26 (25.5)	0.003
Body mass index, kg/m^2	23.8 (3.6)	24.1 (3.5)	24.0 (3.5)	0.052
Current smoking, No. (%)	243 (28.0)	559 (25.3)	14 (13.7)	0.008
Current alcohol drinking, No. (%)	259 (29.8)	597 (27.0)	13 (12.8)	0.001
MTHFR C677T polymorphisms, No. (%)				
CC	261 (30.0)	656 (29.6)	24 (23.5)	0.745
CT	423 (48.6)	1077 (48.6)	53 (52.0)	
TT	186 (21.4)	482 (21.8)	25 (24.5)	
Treatment group, No. (%)				
Enalapril	424 (48.7)	1109 (50.1)	46 (45.1)	0.528
Enalapril-folic acid	446 (51.3)	1106 (49.9)	56 (54.9)	
Baseline BP, mm Hg				
Systolic	152.0 (5.9)	150.6 (6.5)	148.0 (7.6)	<0.001
Diastolic	87.4 (8.2)	87.7 (7.8)	88.4 (7.2)	0.384
Time-averaged BP during the treatment period, mm Hg				
Systolic	147.3 (6.6)	131.5 (5.2)	116.7 (3.0)	<0.001
Diastolic	84.6 (7.1)	79.8 (5.8)	75.2 (5.2)	<0.001
Self-reported hyperlipidemia	15 (1.7)	41 (1.9)	3 (2.9)	0.689
Self-reported diabetes mellitus	21 (2.4)	43 (1.9)	3 (2.9)	0.595
Laboratory results				
Fasting glucose, mmol/L	5.7 (1.9)	5.6 (1.4)	5.5 (1.6)	0.114
Total cholesterol, mmol/L	5.3 (1.1)	5.4 (1.2)	5.4 (1.3)	0.007
Creatinine, μmol/L	64.8 (16.2)	64.3 (15.4)	62.7 (12.6)	0.416
Homocysteine, μmol/L	14.4 (8.3)	13.6 (6.8)	12.9 (5.6)	0.011
Folate, ng/mL	9.4 (4.7)	9.3 (4.3)	9.4 (4.0)	0.591
Medication use, No. (%)				
Lipid-lowering drugs	1 (0.1)	6 (0.3)	0 (0)	0.630
Glucose-lowering drugs	10 (1.2)	21 (1.0)	1 (1.0)	0.880
Antiplatelet drugs	0 (0)	9 (0.4)	1 (1.0)	0.091

BP indicates blood pressure; MTHFR, methylenetetrahydrofolate reductase; SBP, systolic blood pressure.
*Values are presented as mean (SD) for continuous variables.

was reduced to <140/90 mm Hg are summarized in Table 1. From the lowest to the highest proportion of study visits with BP <140/90 mm Hg, participants were less likely to be men and tended to have lower percentages of cigarette smoking and alcohol drinking and lower levels of creatinine and homocysteine. Similar trends were observed when participants were grouped by the time-averaged SBP or DBP levels during the treatment period (Tables 2 and 3).

Primary and Secondary Outcomes According to the Proportion of Visits With BP <140/90 mm Hg

During the study treatment period, a total of 49 participants (1.5%) discontinued the treatments because of adverse reactions. For the primary outcome, the median length of follow-up was 4.6 years (interquartile range, 4.2–4.9). First stroke occurred in 52 participants. Stroke cases could be classified

Table 3. Characteristics of the Study Participants by Time-Averaged DBP Levels* During the Treatment Period

	Time-Averaged DBP, mm Hg				
	≥90 (n=262)	80 to <90 (n=1503)	75 to <80 (n=869)	<75 (n=553)	P Value
Age, y	54.4 (6.6)	57.8 (7.1)	60.9 (6.8)	63.9 (6.4)	<0.001
Male, No. (%)	134 (51.2)	633 (42.1)	321 (36.9)	228 (41.2)	<0.001
Body mass index, kg/m^2	25.1 (3.8)	24.6 (3.5)	23.7 (3.5)	22.7 (3.1)	<0.001
Current smoking, No. (%)	80 (30.5)	373 (24.9)	213 (24.5)	150 (27.1)	0.027
Current alcohol drinking, No. (%)	93 (35.5)	428 (28.5)	201 (23.2)	147 (26.6)	0.005
MTHFR C677T polymorphisms, No. (%)					
CC	79 (30.2)	414 (27.6)	268 (30.8)	180 (32.6)	0.098
CT	119 (45.4)	740 (49.2)	423 (48.7)	271 (49.0)	
TT	64 (24.4)	349 (23.2)	178 (20.5)	102 (18.4)	
Treatment group, No. (%)					
Enalapril	132 (50.4)	726 (48.3)	439 (50.5)	282 (51.0)	0.616
Enalapril-folic acid	130 (49.6)	777 (51.7)	430 (49.5)	271 (49.0)	
Baseline BP, mm Hg					
Systolic	148.4 (8.2)	150.6 (6.6)	151.4 (5.7)	151.8 (5.4)	<0.001
Diastolic	94.1 (4.6)	90.3 (6.3)	86.0 (7.1)	79.8 (7.7)	<0.001
Time-averaged BP during the treatment period, mm Hg					
Systolic	145.7 (10.0)	136.8 (8.7)	132.8 (8.5)	130.6 (8.5)	<0.001
Diastolic	93.9 (3.7)	84.2 (2.7)	77.7 (1.4)	71.5 (3.0)	<0.001
Self-reported hyperlipidemia	2 (0.8)	36 (2.4)	15 (1.7)	6 (1.1)	0.111
Self-reported diabetes mellitus	2 (0.8)	29 (1.9)	22 (2.5)	14 (2.5)	0.287
Laboratory results					
Fasting glucose, mmol/L	5.5 (1.4)	5.6 (1.4)	5.7 (1.7)	5.6 (1.9)	0.240
Total cholesterol, mmol/L	5.3 (1.1)	5.5 (1.2)	5.4 (1.1)	5.4 (1.1)	<0.001
Creatinine, μmol/L	65.6 (14.7)	64.8 (15.0)	63.9 (16.2)	63.9 (16.2)	0.112
Homocysteine, μmol/L	14.1 (10.4)	13.9 (7.7)	13.6 (6.1)	13.5 (5.5)	0.516
Folate, ng/mL	9.2 (4.0)	9.0 (4.4)	9.6 (4.4)	9.8 (4.5)	<0.001
Medication use, No. (%)					
Lipid-lowering drugs	0 (0)	5 (0.3)	2 (0.2)	0 (0)	0.445
Glucose-lowering drugs	1 (0.4)	15 (1.0)	9 (1.0)	7 (1.3)	0.703
Antiplatelet drugs	0 (0)	5 (0.3)	3 (0.4)	2 (0.4)	0.823

BP indicates blood pressure; DBP, diastolic blood pressure; MTHFR, methylenetetrahydrofolate reductase.
*Values are presented as mean (SD) for continuous variables.

into ischemic (n=36) or hemorrhagic stroke (n=16) based on computed tomographic or magnetic resonance imaging findings. Furthermore, a total of 3 cases were fatal stroke.

A median of 16 (interquartile range, 12–18) BP measurements were taken during the treatment period. The association between the proportion of study visits in which BP was <140/90 mm Hg and risk of first stroke are presented in Figure 2. Overall, the risk of stroke decreased with the increase of the proportion of visits with BP <140/90 mm Hg (for per 5% increase; HR,0.92; 95% CI, 0.87–0.98) (Table 4).

The time-averaged SBPs were 151.6, 142.0, 134.4, and 126.1 mm Hg, respectively, in patients with <25%, 25% to 50%, 50% to 75%, and ≥75% of the study visits in which BP was <140/90 mm Hg (Table 1). Compared with participants with <25% of the visits in which BP was <140/90 mm Hg (stroke incidence: 3.7%), the incidence of stroke decreased significantly in those with 25% to 50% (1.8%; HR, 0.47 [95% CI, 0.21–1.05]), 50% to 75% (1.3%; HR, 0.33 [95% CI, 0.15–0.72]), and ≥75% (1.3%; HR, 0.35 [95% CI, 0.15–0.80]) of the visits with BP <140/90 mm Hg (*P* for trend=0.015). Excluding
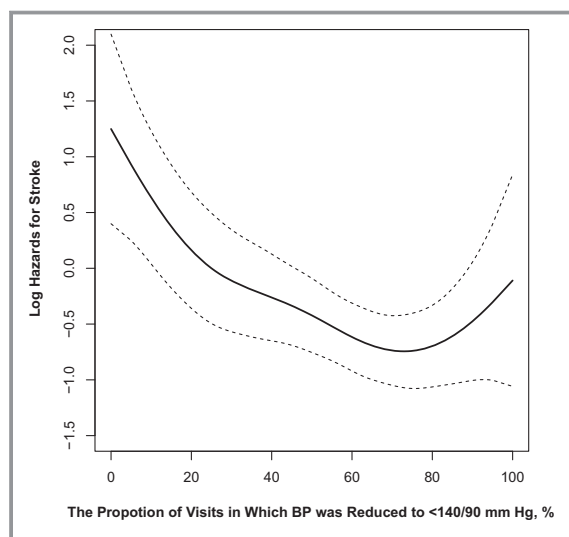
Figure 2. The association between the proportion of study visits in which blood pressure (BP) was <140/90 mm Hg and the risk of first stroke. Adjusted for age, sex, study centers, methylenetetrahydrofolate reductase C677T polymorphism, study treatment groups, body mass index, smoking, alcohol drinking, systolic and diastolic blood pressure, estimated glomerular filtration rate, fasting glucose, total cholesterol, folate, vitamin B12, and homocysteine levels at baseline.

participants with diabetes mellitus (n=321) or estimated glomerular filtration rate <60 mL/min per 1.73 m^2 (n=27) at baseline did not substantially change the results (<25%, 3.8% [reference]; 25–50%, 1.7%; HR, 0.45 [95% CI, 0.19–1.07]; 50–<75%, 1.3%; HR, 0.34 [95% CI, 0.15–0.78]; ≥75%, 1.2%; HR, 0.35 [95% CI, 0.14–0.87]; *P* for trend=0.030). Similar results were observed for the composite cardiovascular events or all-cause death (Table 4).

Primary and Secondary Outcomes According to Time-Averaged BP During the Treatment Period

The association between time-averaged SBP during the treatment period and risk of first stroke followed a U shape, with an increased risk above or below the reference range of 120 to <140 mm Hg (Figure 3). Compared with patients with time-averaged SBP of 120 to <140 mm Hg (mean SBP: 131.5±5.2 mm Hg), the risk of first stroke was significantly higher in participants with time-averaged SBP ≥140 mm Hg (mean SBP: 147.3±6.6 mm Hg; HR, 2.58 [95% CI, 1.46–4.56]) or <120 mm Hg (mean SBP: 116.7±3.0 mm Hg; HR, 3.43 [95% CI, 1.01–11.63]) (Table 5).

Furthermore, compared with patients with time-averaged DBP ≥90 mm Hg (mean DBP: 93.9±3.7 mm Hg), the risk of first stroke was lower in participants with time-averaged DBP <90 mm Hg (mean DBP: 79.8±5.5 mm Hg; HR, 0.41 [95% CI, 0.17–0.98]) (Table 6).

Similar results were observed for the composite cardiovascular events or all-cause death (Figure 4, Tables 5 and 6).

Stratified Analyses for the Primary Outcome

Stratified analyses were performed by sex, age (<60 versus ≥60 years), baseline SBP levels (<150 [mean baseline SBP: 144.9±4.1 mm Hg] versus ≥150 mm Hg [mean: 155.1±3.1 mm Hg]), hypertension subtypes (isolated systolic hypertension or systolic-diastolic hypertension), and study treatment groups (enalapril or enalapril-folic acid group). The lower risk of first stroke was observed in participants with ≥25% of visits in which BP was <140/90 mm Hg (versus <25%) or time-averaged SBP during the treatment period of 120 to <140 mm Hg (versus ≥140 mm Hg) across all subgroups (Figure 5).

Regular concomitant medication was defined as ≥180 cumulative days of taking the drug of interest. The most common concomitant other antihypertensive drugs during the treatment period were dihydropyridine and hydrochlorothiazide, which were used in about 60% and 29% of the participants, respectively. Further adjustment of the concomitant other antihypertensive drugs during treatment period did not substantially change the results (Table 7). Moreover, although multiple imputations were used to deal with missing values in the current study, because of the relatively small number of missing data, the results did not vary meaningfully when missing data were treated as missing without the imputation (Table 8).

Discussion

Two types of data analysis[11] were employed in the current study. First, the incidence and risk of outcomes were assessed according to the proportion of study visits in which BP was reduced to <140/90 mm Hg, to reflect the way physicians determine BP control and modify treatment strategy in real clinical practice. Second, outcomes were calculated according to the time-averaged BP levels during the treatment period. The results of all of these analyses suggested that achieved BP <140/90 mm Hg was significantly associated with decreased risks of stroke and composite of cardiovascular events or all-cause death in patients with grade 1 hypertension and without a history of major cardiovascular diseases. The absolute rate of stroke was relatively small (about 0.35% per year) in our current study. However, compared with participants with <25% of the visits in which BP was <140/90 mm Hg (stroke incidence: 3.7%), the incidence of stroke decreased significantly in those with ≥25% (absolute stroke risk reduction: 2.3%; HR, 0.38 [95% CI, 0.19–0.75]) of the visits with BP<140/90 mm Hg (Figure 5). Both the absolute and the relative risk reductions

Table 4. Primary and Secondary Outcomes According to the Proportion of Visits in Which BP was Reduced to <140/90 mm Hg

Proportion of Visits With BP <140/90 mm Hg	Outcome, No. (%)	HR (95% CI)	Adjusted* HR (95% CI)
Primary outcome			
First stroke			
Continuous: per 5% increase	52 (1.6)	0.92 (0.87–0.97)	0.92 (0.87–0.98)
Categorical			
<25%	11 (3.7)	Ref	Ref
25% to <50%	13 (1.8)	0.46 (0.20–1.02)	0.47 (0.21–1.05)
50% to <75%	16 (1.3)	0.32 (0.15–0.69)	0.33 (0.15–0.72)
≥75%	12 (1.3)	0.33 (0.15–0.76)	0.35 (0.15–0.80)
P for trend		0.011	0.015
Secondary outcomes			
Composite of stroke, myocardial infarction, or death from cardiovascular causes			
Continuous: per 5% increase	61 (1.9)	0.92 (0.88–0.97)	0.92 (0.88–0.97)
Categorical			
<25%	13 (4.4)	Ref	Ref
25% to <50%	15 (2.1)	0.45 (0.21–0.94)	0.45 (0.21–0.95)
50% to <75%	19 (1.5)	0.32 (0.16–0.65)	0.32 (0.16–0.65)
≥75%	14 (1.5)	0.33 (0.15–0.70)	0.33 (0.15–0.71)
P for trend		0.006	0.007
All-cause death			
Continuous: per 5% increase	87 (2.7)	0.94 (0.90–0.98)	0.95 (0.90–0.99)
Categorical			
<25%	15 (5.2)	Ref	Ref
25% to <50%	21 (2.9)	0.54 (0.28–1.05)	0.55 (0.28–1.08)
50% to <75%	31 (2.5)	0.46 (0.25–0.84)	0.46 (0.24–0.86)
≥75%	20 (2.2)	0.41 (0.21–0.80)	0.46 (0.23–0.91)
P for trend		0.016	0.040

BP indicates blood pressure; HR, hazard ratio.
*Adjusted for age, sex, study centers, methylenetetrahydrofolate reductase C677T polymorphism, study treatment groups, body mass index, smoking, alcohol drinking, systolic and diastolic blood pressure, estimated glomerular filtration rate, fasting glucose, total cholesterol, folate, vitamin B12, and homocysteine levels at baseline.

were considerable. More important, the beneficial results were consistent across age, sex, baseline SBP, hypertension subtypes, and treatment groups. In addition, only 1.5% of the participants discontinued the treatments because of adverse reaction. Since a large proportion of hypertensive patients are individuals with grade 1 hypertension and without cardiovascular disease, our findings have important implications.

A previous meta-analysis[3] of 4 randomized trials, including 8912 participants, found that antihypertensive treatment for adults with grade 1 hypertension did not reduce mortality or cardiovascular disease risk. However, a recent meta-analysis[12] including 6361 additional participants from the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) data sets concluded that BP-lowering therapy was likely to prevent stroke and death in patients with uncomplicated

grade 1 hypertension. Nevertheless, most of the patients in BPLTTC trials had diabetes mellitus and were under antihypertensive treatment at baseline. These results indicate that many of the high-risk patients (with diabetes mellitus) in BPLTTC trials—if untreated—may have been above the range defining grade 1 hypertension. The recent meta-analysis conducted by Thomopoulos et al[13] included trials or trial subgroups with mean baseline SBP/DBP levels in grade 1 hypertension's definition range and a low to moderate risk (<5% cardiovascular deaths in 10 years in controls): Felodipine Event Reduction (FEVER) stratum with baseline SBP below the median (mean baseline SBP/DBP: 144/89 mm Hg and with baseline antihypertensive treatments)[14]; Hypertension Detection and Follow-up Program [HDFP] stratum with baseline DBP 90 to 94 mm Hg[15]; OSLO[16]; Treatment of Mild
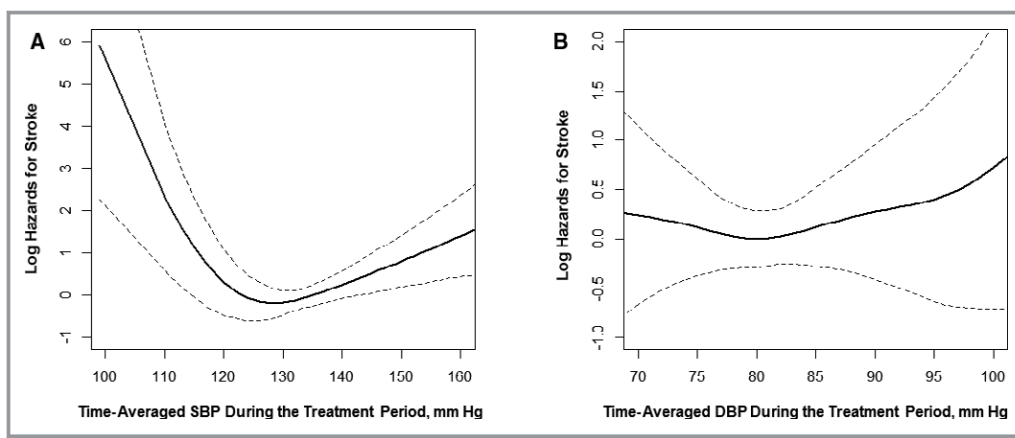
Figure 3. The association between time-averaged systolic blood pressure (SBP) (A) or diastolic blood pressure (DBP) (B) during the treatment period and risk of first stroke. Adjusted for age, sex, study centers, methylenetetrahydrofolate reductase C677T polymorphism, study treatment groups, body mass index, smoking, alcohol drinking, systolic and diastolic blood pressure, estimated glomerular filtration rate, fasting glucose, total cholesterol, folate, vitamin B12, and homocysteine levels at baseline.

Hypertension Study (TOMHS); mean baseline SBP/DBP: 140/91 mm Hg)[17]; and US Public Health Service (USPHS).[18] This meta-analysis suggested that BP-lowering treatment significantly decreased the risk of stroke, coronary events, and all-cause death. These results provided stronger support to the recommendation to initiate drug treatment in patients with grade 1 low to moderate risk hypertension. However, stratification of trials in grades according to the mean baseline SBP/DBP values was just an approximation.[19] The

trials included in the meta-analyses, especially the Oslo (mean baseline SBP/DBP: 157/97 mm Hg)[16] and USPHS (mean baseline SBP/DBP: 147/99 mm Hg)[18] studies may include a number of patients with baseline BP higher than the current definition for grade 1 hypertension (untreated SBP of 140–159 mm Hg and/or DBP of 90–99 mm Hg). Therefore, extrapolation of the findings from these meta-analyses to uncomplicated grade 1 hypertension patients remains to be determined.

Table 5. Primary and Secondary Outcomes by Time-Averaged SBP Levels During the Treatment Period

Time-Averaged SBP Category, mm Hg	Outcome, No. (%)	HR (95% CI)	Adjusted* HR (95% CI)
Primary outcome			
First stroke			
<120	3 (2.9)	2.84 (0.85–9.43)	3.43 (1.01–11.63)
120 to <140†	24 (1.1)	Ref	Ref
≥140	25 (2.9)	2.73 (1.56–4.77)	2.58 (1.46–4.56)
Secondary outcomes			
Composite of stroke, myocardial infarction, or death from cardiovascular causes			
<120	4 (3.9)	3.12 (1.10–8.87)	3.80 (1.31–11.01)
120 to <140	29 (1.3)	Ref	Ref
≥140	28 (3.2)	2.52 (1.50–4.24)	2.37 (1.40–4.02)
All-cause death			
<120	5 (5.0)	2.46 (0.98–6.18)	3.41 (1.34–8.67)
120 to <140	47 (2.1)	Ref	Ref
≥140	35 (4.1)	1.94 (1.25–3.01)	1.63 (1.05–2.55)

SBP indicates systolic blood pressure.
*Adjusted for age, sex, study centers, methylenetetrahydrofolate reductase C677T polymorphism, study treatment groups, body mass index, smoking, alcohol drinking, systolic and diastolic blood pressure, estimated glomerular filtration rate, fasting glucose, total cholesterol, folate, vitamin B12, and homocysteine levels at baseline.
†Versus ≥140 mm Hg; adjusted hazard ratio (HR), 0.39; 95% CI, 0.22–0.69.

Table 6. Primary and Secondary Outcomes by Time-Averaged DBP During the Treatment Period

Time-Averaged DBP Category, mm Hg	Outcome, No. (%)	HR (95% CI)	Adjusted* HR (95% CI)
Primary outcome			
First stroke			
≥90	7 (2.7)	Ref	Ref
<90	45 (1.5)	0.56 (0.25–1.24)	0.41 (0.17–0.98)
80 to <90	23 (1.5)	0.56 (0.24–1.30)	0.45 (0.18–1.09)
75 to <80	10 (1.2)	0.41 (0.16–1.09)	0.29 (0.10–0.83)
<75	12 (2.2)	0.78 (0.31–1.99)	0.46 (0.14–1.50)
Secondary outcomes			
Composite of stroke, myocardial infarction, or death from cardiovascular causes			
≥90	8 (3.0)	Ref	Ref
<90	53 (1.8)	0.57 (0.27–1.20)	0.37 (0.16–0.84)
80 to <90	26 (1.7)	0.55 (0.25–1.21)	0.41 (0.18–0.94)
75 to <80	11 (1.3)	0.40 (0.16–0.99)	0.25 (0.09–0.69)
<75	16 (2.9)	0.90 (0.39–2.11)	0.49 (0.17–1.41)
All-cause death			
≥90	7 (2.7)	Ref	Ref
<90	80 (2.7)	0.98 (0.45–2.13)	0.66 (0.29–1.50)
80 to <90	35 (2.3)	0.85 (0.38–1.91)	0.69 (0.30–1.59)
75 to <80	24 (2.7)	0.98 (0.42–2.28)	0.60 (0.24–1.49)
<75	21 (3.8)	1.34 (0.57–3.17)	0.60 (0.22–1.61)

DBP indicates diastolic blood pressure; HR, hazard ratio.

*Adjusted for age, sex, study centers, methylenetetrahydrofolate reductase C677T polymorphism, study treatment groups, body mass index, smoking, alcohol drinking, systolic and diastolic blood pressure, estimated glomerular filtration rate, fasting glucose, total cholesterol, folate, vitamin B12, and homocysteine levels at baseline.

The time-averaged SBPs during the treatment period were 151.6, 142.0, 134.4, and 126.1 mm Hg in patients with <25%, 25% to 50%, 50% to 75%, and ≥75%, respectively, of the study visits in which BP was reduced to <140/90 mm Hg (Table 1). The greatest reduction in risk (primary or secondary outcomes, about 2% of the absolute risk reduction) always occurred when the proportion of visits with BP <140/90 mm Hg progressed from <25% to 25–<50%, with a further
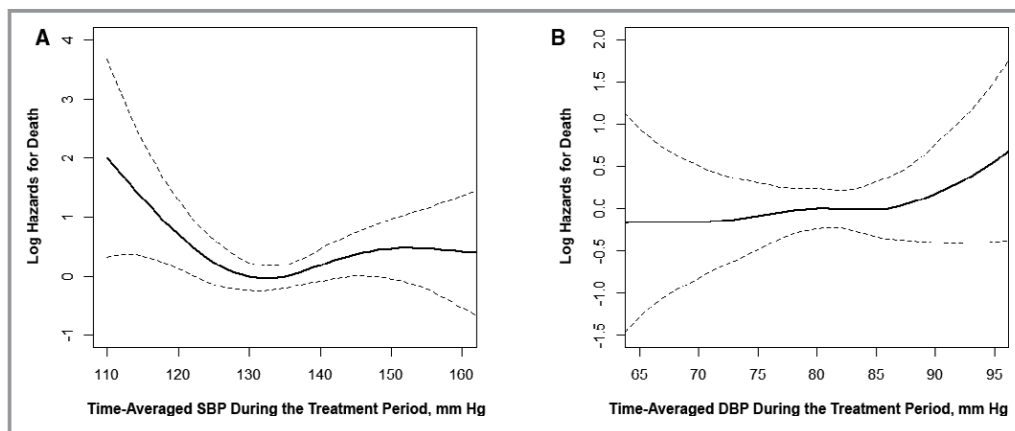

Figure 4. The association between time-averaged systolic blood pressure (SBP) (A) or diastolic blood pressure (DBP) (B) during the treatment period and risk of all-cause death. Adjusted for age, sex, study centers, methylenetetrahydrofolate reductase C677T polymorphism, study treatment groups, body mass index, smoking, alcohol drinking, SBP and DBP, estimated glomerular filtration rate, fasting glucose, total cholesterol, folate, vitamin B12, and homocysteine levels at baseline.
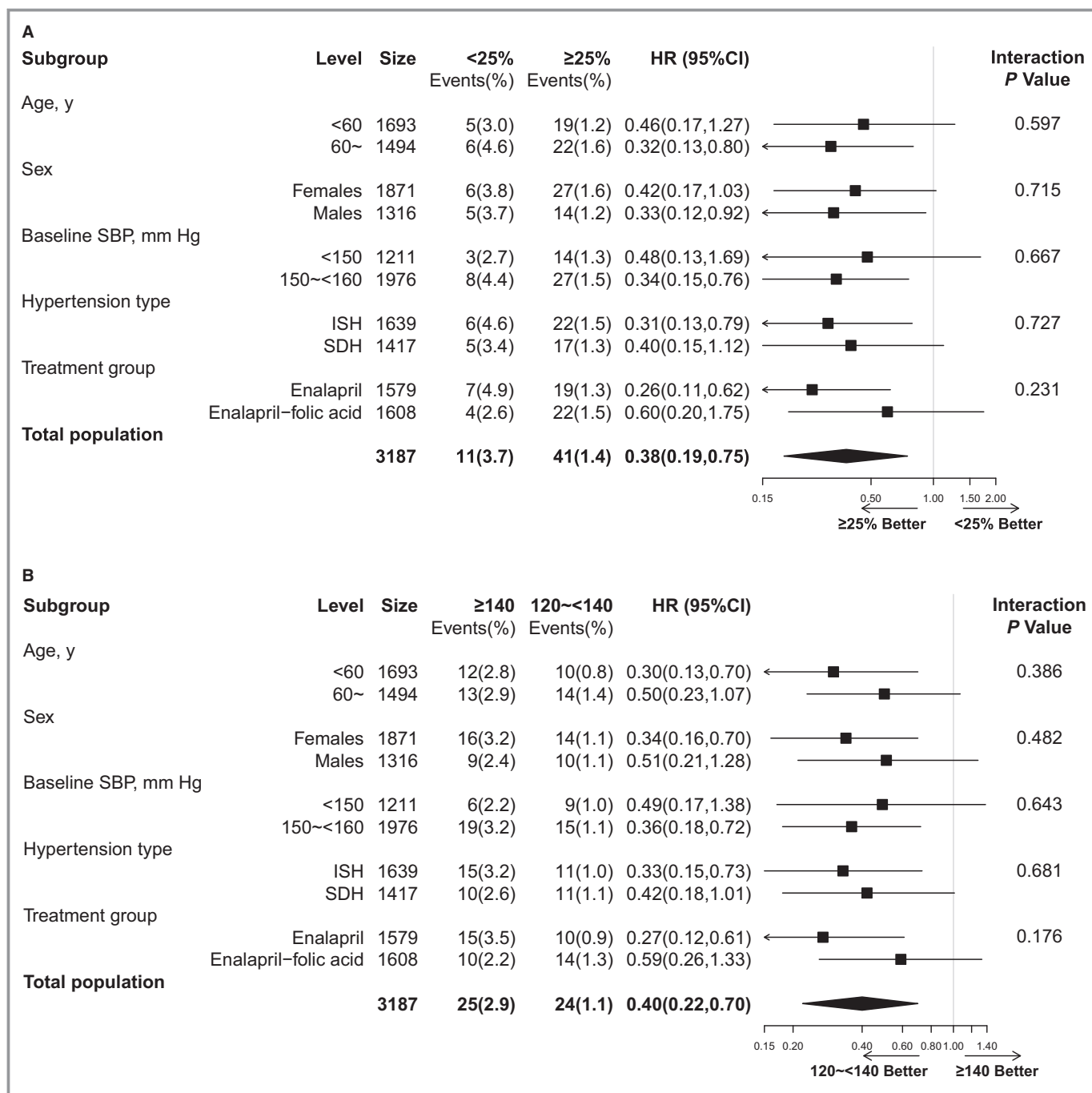
A

Subgroup	Level	Size	<25% Events(%)	≥25% Events(%)	HR (95%CI)		Interaction P Value
Age, y							
	<60	1693	5(3.0)	19(1.2)	0.46(0.17,1.27)		0.597
	60~	1494	6(4.6)	22(1.6)	0.32(0.13,0.80)		
Sex							
	Females	1871	6(3.8)	27(1.6)	0.42(0.17,1.03)		0.715
	Males	1316	5(3.7)	14(1.2)	0.33(0.12,0.92)		
Baseline SBP, mm Hg							
	<150	1211	3(2.7)	14(1.3)	0.48(0.13,1.69)		0.667
	150~<160	1976	8(4.4)	27(1.5)	0.34(0.15,0.76)		
Hypertension type							
	ISH	1639	6(4.6)	22(1.5)	0.31(0.13,0.79)		0.727
	SDH	1417	5(3.4)	17(1.3)	0.40(0.15,1.12)		
Treatment group							
	Enalapril	1579	7(4.9)	19(1.3)	0.26(0.11,0.62)		0.231
	Enalapril−folic acid	1608	4(2.6)	22(1.5)	0.60(0.20,1.75)		
Total population		3187	11(3.7)	41(1.4)	0.38(0.19,0.75)		

0.15   0.50   1.00   1.50 2.00
≥25% Better   <25% Better

B

Subgroup	Level	Size	≥140 Events(%)	120~<140 Events(%)	HR (95%CI)		Interaction P Value
Age, y							
	<60	1693	12(2.8)	10(0.8)	0.30(0.13,0.70)		0.386
	60~	1494	13(2.9)	14(1.4)	0.50(0.23,1.07)		
Sex							
	Females	1871	16(3.2)	14(1.1)	0.34(0.16,0.70)		0.482
	Males	1316	9(2.4)	10(1.1)	0.51(0.21,1.28)		
Baseline SBP, mm Hg							
	<150	1211	6(2.2)	9(1.0)	0.49(0.17,1.38)		0.643
	150~<160	1976	19(3.2)	15(1.1)	0.36(0.18,0.72)		
Hypertension type							
	ISH	1639	15(3.2)	11(1.0)	0.33(0.15,0.73)		0.681
	SDH	1417	10(2.6)	11(1.1)	0.42(0.18,1.01)		
Treatment group							
	Enalapril	1579	15(3.5)	10(0.9)	0.27(0.12,0.61)		0.176
	Enalapril−folic acid	1608	10(2.2)	14(1.3)	0.59(0.26,1.33)		
Total population		3187	25(2.9)	24(1.1)	0.40(0.22,0.70)		

0.15 0.20   0.40   0.60 0.80 1.00   1.40
120~<140 Better   ≥140 Better

Figure 5. Primary outcome according to the proportion of visits in which blood pressure was <140/90 mm Hg (≥25% vs <25%) (A) or time-averaged systolic blood pressure (SBP) during the treatment period (120 to <140 mm Hg vs ≥140 mm Hg) (B) in various subgroups. Adjusted for age, sex, study centers, methylenetetrahydrofolate reductase C677T polymorphism, study treatment groups, body mass index, smoking, alcohol drinking, SBP and DBP, estimated glomerular filtration rate, fasting glucose, total cholesterol, folate, vitamin B12, and homocysteine levels at baseline. HR indicates hazard ratio; ISH, isolated systolic hypertension; SDH, systolic-diastolic hypertension.

modest reduction when the proportion increased from 25–<50% to 50–<75% (about 0.5% of the absolute risk reduction), and with no further obvious reduction or a slight increase when the proportion increased to from 50–<75% to ≥75%. These results suggested that in patients with grade 1 hypertension and without cardiovascular diseases, more

aggressive SBP reduction may not offer substantial advantages. Accordingly, our study also suggested that the risk of first stoke, composite of cardiovascular events, or all-cause death were all significantly increased in participants with time-averaged SBPs <120 mm Hg, compared with those with time-averaged SBPs of 120 to <140 mm Hg. Consistent with our

Table 7. Impact of Achieved BP on First Stroke in Multivariate-Adjusted Models Including Concomitant Other Antihypertensive Drugs During the Treatment Period

Variables	Outcome, No. (%)	Adjusted* HR (95% CI)
Proportion of visits with BP <140/90 mm Hg		
<25%	11 (3.7)	Ref
25% to <50%	13 (1.8)	0.46 (0.21–1.04)
50% to <75%	16 (1.3)	0.32 (0.15–0.70)
≥75%	12 (1.3)	0.34 (0.14–0.80)
P for trend		0.015
Time-averaged SBP, mm Hg		
<120	3 (2.9)	3.48 (1.00–12.06)
120 to <140	24 (1.1)	Ref
≥140	25 (2.9)	2.63 (1.47–4.73)
Time-averaged DBP, mm Hg		
≥90	7 (2.7)	Ref
<90	45 (1.5)	0.40 (0.17–0.98)
80 to <90	23 (1.5)	0.46 (0.14–1.50)
75 to <80	10 (1.2)	0.28 (0.09–0.83)
<75	12 (2.2)	0.44 (0.18–1.09)

BP indicates blood pressure; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.
*Adjusted for age, sex, study centers, methylenetetrahydrofolate reductase C677T polymorphism, study treatment groups, body mass index, smoking, alcohol drinking, systolic and diastolic blood pressure, estimated glomerular filtration rate, fasting glucose, total cholesterol, folate, vitamin B12, and homocysteine levels at baseline, as well as concomitant use of calcium channel blockers and diuretics during the treatment period.

Table 8. Impact of Achieved BP on First Stroke Without Missing Data Imputation

Variables	Outcome, No. (%)	Adjusted* HR (95% CI)
Proportion of visits with BP<140/90 mm Hg		
<25%	11 (3.8)	Ref
25% to <50%	13 (1.8)	0.48 (0.21–1.07)
50% to <75%	16 (1.3)	0.33 (0.15–0.73)
≥75%	12 (1.4)	0.36 (0.16–0.83)
P for trend		0.018
Time-averaged SBP, mm Hg		
<120	3 (3.1)	3.44 (1.02–11.64)
120 to <140	24 (1.1)	Ref
≥140	25 (2.9)	2.56 (1.45–4.52)
Time-averaged DBP, mm Hg		
≥90	7 (2.7)	Ref
<90	45 (1.6)	0.41 (0.17–1.00)
80 to <90	23 (1.6)	0.48 (0.15–1.54)
75 to <80	10 (1.2)	0.29 (0.10–0.86)
<75	12 (2.2)	0.46 (0.19–1.12)

BP indicates blood pressure; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.
*Adjusted for age, sex, study centers, methylenetetrahydrofolate reductase C677T polymorphism, study treatment groups, body mass index, smoking, alcohol drinking, systolic and diastolic blood pressure, estimated glomerular filtration rate, fasting glucose, total cholesterol, folate, vitamin B12, and homocysteine levels at baseline.

results, some of the previous studies found that an SBP <120 mm Hg was associated with an increased risk of stroke (versus 130–<140 mm Hg; Prevention Regimen For Effectively Avoiding Second Strokes [PROFESS] trial[20]) or all-cause death (versus 120–130 mm Hg; the International Verapamil SR-Trandolapril Study [INVEST][21]). However, targeting an SBP of <120 mm Hg (intensive group), compared with <140 mm Hg (standard group), has been reported to result in lower rates of stroke in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[22] and lower rates of composite cardiovascular events in Systolic Blood Pressure Intervention Trial (SPRINT).[23] The possible explanations for these inconsistent results may be that, first, the average SBP in the intensive treatment group were 119.3 and 121.4 mm Hg in the ACCORD and SPRINT trials, respectively, which indicated that many of the participants in the intensive group did not reach the goal of an SBP <120 mm Hg, and instead may have had an SBP of 120 to <130 mm Hg. Second, it has been argued that, if measured by the usual office technique, the SPRINT BP values would likely be higher than those reported.[19,24] Third, common sense indicates that

a J curve must exist for BP. However, the "nadir" SBP values may possibly vary in hypertensive patients with different ethnic backgrounds or concomitant baseline diseases. We agree that the controversy of "the lower the better" versus the J curve can only be solved by a series of well-designed randomized trials, such as the ongoing Stroke in Hypertension Optimal Treatment (SHOT) study.[25] Nevertheless, our current findings emphasize that patients with grade 1 hypertension should possibly avoid excessive SBP reduction during treatment.

Furthermore, it has been recognized that most of the previous trials showing the benefits of antihypertensive treatment in the elderly or in patients with isolated systolic hypertension have enrolled participants with baseline SBP ≥160 mm Hg (grade 2 or 3 hypertension).[4] In our current analysis, the lower risk of first stroke was found in participants with ≥25% of the visits in which BP was <140/90 mm Hg (versus <25%) or time-averaged SBP during the treatment period at 120 to <140 mm Hg (versus ≥140 mm Hg) in subgroups with different ages (<60 versus ≥60 years), different baseline SBP levels (<150 versus ≥150 mm Hg), and different hypertension subtypes (isolated systolic hypertension or systolic-diastolic hypertension). However, these results still warrant further confirmation.

Study Limitations

This study has several limitations. First, this was a post hoc analysis of the CSPPT. Despite extensive adjustments for known factors and the benefits being consistent across different outcomes, we could not exclude the possibility that unrecorded risk factors may explain some of our findings. Second, only a small number of patients had a time-averaged SBP <120 mm Hg or a time-averaged DBP ≥90 mm Hg, which means that comparisons of the risk of study outcomes involved groups of markedly different sizes, some of which were small. Third, because of the small numbers of events, we could not determine the optimal BP levels below 140/90 mm Hg in grade 1 hypertension. Furthermore, the time-averaged BP reflects the effect of long-term control of BP. The major problem with time-averaged BP is the difficulty in implementing it shortly after the start of treatment. It will take some time to have a good idea of a patient's time-averaged BP in a prospective context. Overall, the CSPPT was not specifically designed to determine the BP goal for preventing cardiovascular diseases. Our current results indicate the possible beneficial or detrimental effect when the long-term averaging BP was reduced to a certain level. Therefore, confirmation of our findings in a large-scale clinical trial of randomized participants with uncomplicated grade 1 hypertension to different BP targets is essential.

Conclusions

Among patients with grade 1 hypertension and without cardiovascular diseases, achieved BP <140/90 mm Hg was significantly associated with a decreased risk of stroke or all-cause death both when data were calculated as a proportion of visits with BP <140/90 mm Hg or as on-treatment time-averaged BP.

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Disclosures

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