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Effect of Intensive Blood Pressure Control on Carotid Morphology and Hemodynamics in Chinese Patients with Hyperhomocysteinemia-Type Hypertension and High Risk of Stroke

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Background: Different blood pressure targets should be formulated for different groups of people. This study aimed to assess the effectiveness of intensive blood control in improving the carotid morphology and hemodynamics in Chinese patients with hyperhomocysteinemia-type hypertension and high risk of stroke.

Material/Methods: Chinese hypertensive patients with high risk of stroke were randomized to intensive (n=187) and standard (n=192; controls) blood pressure management groups. Systolic blood pressure (SBP) targets were 100< SBP ≤120 and 120< SBP ≤140 mmHg, respectively. All patients received folic acid 0.8 mg/d and atorvastatin 20 mg/d. Calcium antagonist was first used. If blood pressure was still uncontrolled, angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist, β-receptor blocker, and diuretics were added successively. Follow-up was 12 months. Carotid features, hemodynamics, and adverse events were examined.

Results: There were no differences in sex, age, body mass index, blood lipids, baseline carotid parameters, and histories of smoking, diabetes, statin use, and stroke between the 2 groups. Carotid plaques after 12 months of treatment were 19.4±2.1 and 23.6±3.1 cm^2 for the intensive and control groups, respectively (P=0.038). Plaque scores were lower in the intensive group (1.75±0.52 *vs.* 2.45±0.47, P=0.023). Compared with controls, intensive management resulted in relatively higher Vd and significantly lower Vs/Vd, PI, and RI (all P<0.05). Major adverse events such as hypotension (n=5 (2.7%) *vs.* 3 (1.6%), P=0.020) and dizziness (n=20 (10.7%) *vs.* 16 (8.3%), P=0.041) were more frequent in the intensive group.

Conclusions: Intensive blood pressure management could be beneficial for Chinese patients with hyperhomocysteinemia-type hypertension and high risk of stroke.

MeSH Keywords: Hypertension • Risk • Stroke

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Background

Hypertension with hyperhomocysteinemia, or 'H-type hypertension' (serum homocysteine, Hcy ≥10 μmol/L), is an important risk factor for cardiovascular events and stroke [1]. Its incidence is significantly higher in China compared with other countries, representing 75% of Chinese patients with hypertension [2]. In addition, significantly elevated stroke incidence and mortality are found in China compared with global averages, despite lower coronary heart disease incidence and mortality [3]. Low rates of awareness, treatment, and control rates of hypertension in China can also be involved in the epidemiology of stroke [4]. Patients with H-type hypertension are advised to consume folate-rich foods as a general lifestyle intervention for hypertension and to take supplemental folic acid in combination with blood pressure control [2,5]. A meta-analysis in 2007 [6] indicated that folic acid supplementation could decrease the risk of stroke by 18% in patients with H-type hypertension and high-risk factors for stroke, corroborating another meta-analysis [7]. A randomized, double-blind, controlled CSPPT clinical trial which assessed 20 702 adult hypertensive patients in China (without stroke or myocardial infarction) comprised 2 groups receiving enalapril maleate10 mg and folic acid 0.8 mg *vs.* enalapril maleate only (10 mg); after 4.5 years of follow-up, blood pressure was similar in both groups, but the risk of first stroke was decreased by 21% in patients receiving enalapril maleate and folic acid [8]. In addition, the composite cardiovascular event (cardiovascular death, myocardial infarction, and stroke) and ischemic stroke rates were reduced by 20% and 24%, respectively [8].

Nevertheless, the target for blood pressure control in H-type hypertension remains unclear due to insufficient evidence from large randomized trials. Current evidence-based guidelines for the management of high blood pressure in adults, such as those released by the European Society of Cardiology (ESC) in 2013 [9] and the Eighth Joint National Committee (JNC 8) in 2014 [10], recommend a loose goal for blood pressure control. It was emphasized that individualized blood pressure targets should be considered for different cohorts and there is a need for guideline updates in China [4]. In addition, previous studies indicated that intensive blood pressure control could benefit patients with certain types of hypertension [11–14].

It is known that carotid atherosclerotic plaques, carotid intima-media thickness (IMT), and hemodynamic features can be used to evaluate the severity of atherosclerotic diseases, and these indicators are of predictive value for cardiovascular events [15,16].

Because data regarding blood pressure targets in H-type hypertension are lacking, the present study aimed to assess whether intensive blood pressure management could improve the morphologic features of the carotids and the hemodynamics in patients with H-type hypertension and high risk of stroke. The resulting findings could provide valuable evidence for larger clinical trials focusing on hypertension management.

Material and Methods

Study design and patients

This was a randomized, open-label, controlled trial of consecutive patients with H-type hypertension who visited the Department of Cardiology of China-Japan Friendship Hospital between January 2013 and October 2015. The study was approved by the Ethics Committee of China-Japan Friendship Hospital (ethics approval number: 2015-107). Signed written informed consent was obtained from all patients. This study was registered (#ChiCTR-INR-16009437).

The inclusion criteria were according to those of the ACCORD study [11]: 1) ≤75 years of age; 2) H-type primary hypertension (serum Hcy >10 μmol/L) [1]; and 3) at least 1 high-risk factor for stroke among the following: a) ≥40 years old with peripheral arterial disease or a history of TIA/ischemic stroke; b) diabetes; c) TT genotype for the methylenetetrahydrofolate reductase (MTHFR) gene; and d) ≥55 years old and with at least 2 confirmed factors among: atherosclerosis, proteinuria, left ventricular hypertrophy, dyslipidemia, smoking, obesity, fibrinogen >3 g/L, and C-reactive protein (CRP) >10 mg/L.

The exclusion criteria were: 1) severe hypertension (mean sitting diastolic BP (msDBP) ≥110 mmHg and/or mean sitting systolic BP (msSBP) ≥180 mmHg); 2) secondary hypertension with a history or evidence of renal parenchymal hypertension; 3) renal vascular hypertension; 4) aortic constriction; 5) primary aldosterone; 6) Cushing's syndrome; 7) pheochromocytoma; 8) drug-induced hypertension; 9) treatment with >3 anti-hypertensive drugs; 10) confirmed postural hypotension; 11) isolated systolic hypertension; 12) acute stroke; 13) confirmed myocardial infarction; 14) history of severe coronary artery disease; 15) carotid artery stenosis >50%; 16) severe liver and kidney dysfunction; 17) life expectancy <5 years; 18) poor treatment compliance; 19) substance abuse; or 20) any other conditions considered by the investigators to be unsuitable for participation.

Randomization

The patients were randomized 1: 1 to the intensive and routine management groups using sequential sealed envelopes prepared by an independent statistician using a random number table. The envelopes were opened sequentially once the patients consented.

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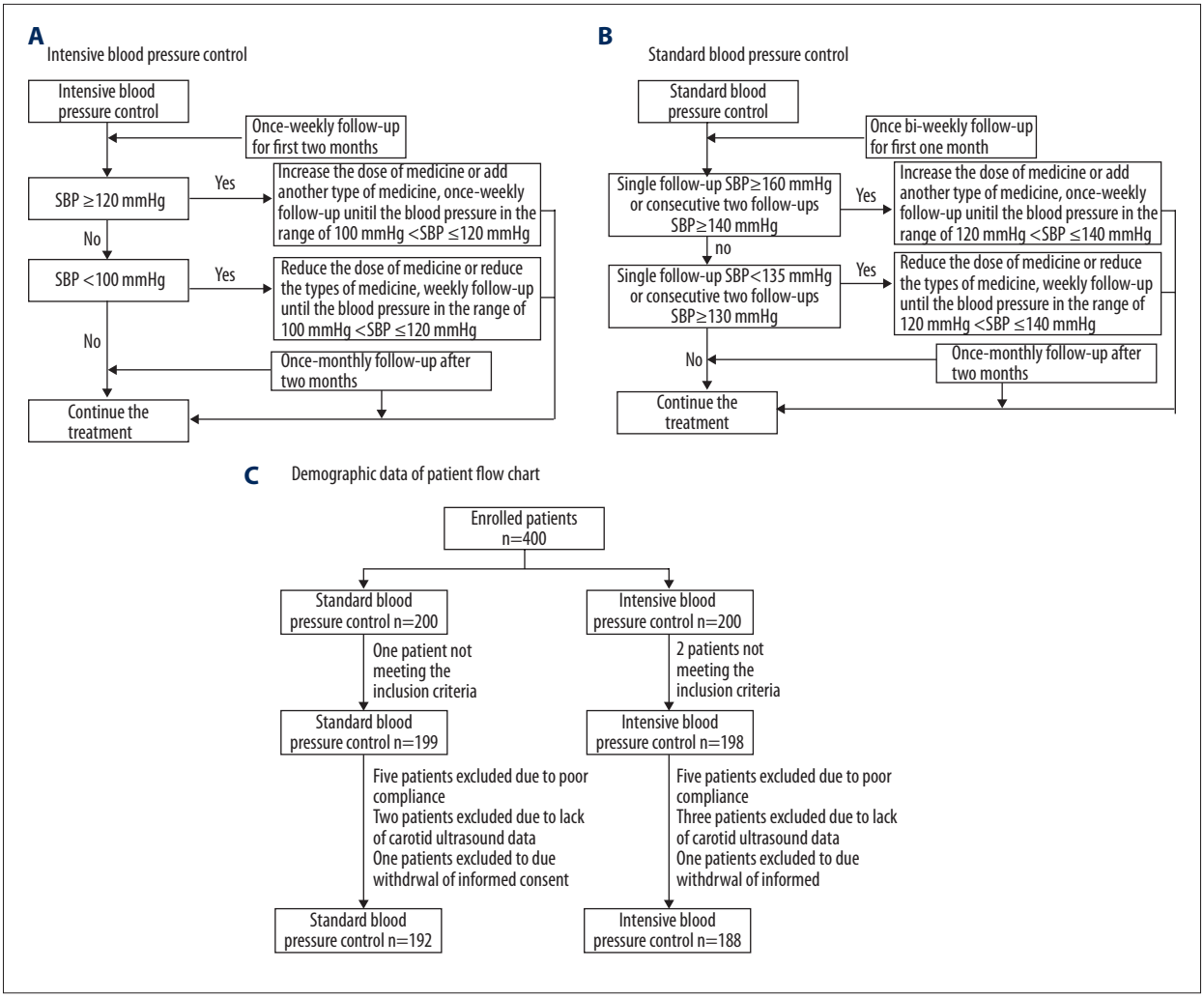

Figure 1. (**A**) Management algorithm in the intensive group. (**B**) Management algorithm in the routine group. (**C**) Patient flowchart.

Intervention

Systolic blood pressure (SBP) targets were 100< SBP ≤120 and 120< SBP ≤140 mmHg in the intensive and routine management groups, respectively, according to the ACCORD trial [11]. All patients received folic acid at 0.8 mg daily and atorvastatin 20 mg daily [17]. Firstly, amlodipine 5 mg qd was used. If blood pressure (BP) did not meet the targets, it was increased to 10 mg qd. Then, perindopril 4 mg qd was added if the BP still could not meet the targets. The dose was increased to 8 mg qd if the BP could not meet the targets. Losartan 50 mg qd was given and could be increased to 100 mg qd if the patient experienced cough. If the BP still did not meet the targets, metoprolol or hydrochlorothiazide was used, according to heart rate conditions. The principles for dose reduction were contrary to those of dosing escalation.

For patients receiving routine management, SBP ≥160 mmHg at 1 follow-up examination or SBP ≥140 mmHg at 2 consecutive follow-ups prompted us to increase medication dose or to add another anti-hypertension drug. When SBP was <130 mmHg at 1 follow-up or SBP was <135 mmHg at 2 consecutive follow-ups, the medication dose was decreased (Figure 1B). In the intensive group, SBP ≥120 mmHg at any time prompted increased medication dose or addition of other anti-hypertensive drugs (Figure 1A).

The investigator made decisions regarding addition and reduction of doses, and whether or not to withdraw the patient from the study according to the patient's conditions. Treatment was discontinued during the trial when any of the following occurred (intent-to-treat (ITT) analysis): 1) follow-up DBP <60 mmHg at any time; 2) intolerable adverse effects such as dizziness caused by hypotension in the intensive management group; 3) informed consent withdrawal; 4) poor compliance; or 5) any other condition that the investigator considered as a termination point.

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Follow-up

The intensive management group was evaluated for BP weekly for the first 2 months, followed by monthly assessments afterwards. Control patients were evaluated for BP weekly for the first month, and once a month afterwards. BP and the endpoints were assessed. Anti-hypertensive drugs were adjusted at each visit according to the BP readings. All patients were instructed to perform self-blood pressure measurement (SBPM) at home. The last follow-up time was October 20th, 2016. The rate of loss to follow-up was 4.3%.

Management of adverse events

The patients were trained for blood pressure monitoring at home, and advised to contact their physician timely if SBP was <100 mmHg or DBP was <60 mmHg, or if they experienced dizziness. In this study, the main adverse effects included: hypotension, bradycardia, electrolyte imbalance, dizziness, and abnormal kidney function.

Endpoints

Carotid plaque area was assessed as the primary study endpoint. The secondary study endpoints included plaque score, IMT, IMT/D, peak systolic velocity (Vs), end-diastolic velocity (Vd), pulsatility index (PI), resistance index (RI), Vs/Vd, and stroke occurrence. PI is the difference between maximum and minimum blood velocity, and is calculated as PI=(Vs–Vd)/Vm, where Vm=(Vs+Vd)/2 [18]. RI is a measure of pulsatile blood flow that reflects the resistance to blood flow caused by the vascular bed distal to the measurement site. RI is calculated as (Vs–Vd)/Vs [19].

Blood pressure measurement

Blood pressure was measured in the sitting position, 3 times, at 5-min intervals, and by the same clinician. Two DBP readouts with a difference <4 mmHg were used. The patient rested for at least 15 min before measurements, with no strong tea or coffee consumed within 30 min. A mercury sphygmomanometer was used for blood pressure measurement. The readouts at first and fifth sounds of the Korotkoff phase were considered systolic and DBP, respectively. When the pulse sound remained until the mercury sphygmomanometer showed 0 mmHg, the readout at the fourth sound of Korotkoff phase was used as DBP.

Carotid plaque assessment

For carotid plaque assessment, plaque was defined as: 1) local bulge protruding out of the arterial lumen by >0.5 mm or >50% of the surrounding IMT; or 2) IMT >1.5 mm. Measurements were made in magnified longitudinal views of each plaque seen in the right and left common, internal, and external carotid arteries. The plane in which the measurement of each plaque was made was chosen by panning around the artery until the view showing the largest extent of plaque was obtained. The image was then frozen and magnified, and the plaque was measured by tracing around the perimeter with a cursor on the screen. The built-in software in the scanner then displayed the cross-sectional area of the plaque. The operator then moved on to the next plaque and repeated the process until all visible plaques were measured. The sum of the cross-sectional areas of all plaques seen between the clavicle and the angle of the jaw was taken as the total plaque area (cm^2) [20]. Regardless of the actual plaque length, maximum thicknesses for plaques isolated from the same carotid were added to obtain the Crouse score, as previously described [21]. All measurements and calculations were carried out by the same ultrasound physician (8 years of experience) using a Siemens digital color Doppler ultrasound diagnostic instrument, with a probe frequency of 7.5 MHz. The patient was placed in the supine position, with back to the examiner. The carotid was scanned sequentially from superior to inferior, and 3 measurements were obtained beneath the lateral branch of the common carotid artery at about 1.0 cm. The IMT value was the average measurement of the 3 time points. The internal diameter (D) of the carotid was measured to derive IMT/D.

For carotid hemodynamic measurement, the major intracranial vessels were scanned using a pulsed Doppler probe at a frequency of 2.0 MHz through the temporal, ocular, and occipital windows. The carotid artery was examined using a probe at a frequency of 4.0 MHz in combination with common carotid artery compression. Blood flow rate, spectrum shape, and resistance index of all arteries were recorded. The anterior cerebral circulation of the middle cerebral artery was recorded. The Vs, Vd, PI [PI=(Vs–Vd)/Vm], RI [RI=Vs–Vd)/Vs], and Vs/Vd were obtained. The whole procedure was performed by the same clinician before the treatment and 1 year after the treatment.

Sample size calculation

This was a single-center, prospective, randomized trial with a statistical power of 80% and bilateral significance level of 0.05. Considering the main efficacy variable of 0.05 cm^2, differences among treatments of 0.05 cm^2 [20], and a loss rate of 5%, the PASS software yielded a sample number of n=280.

Statistical analysis

SPSS 17.0 (IBM, Armonk, NY, USA) was used for statistical analyses. All data were tested using the Shapiro-Wilk normality test. If normally distributed, data were expressed as means ± standard deviation (SD) and compared using the

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Table 1. Demographic and clinical data in the 2 treatment groups at enrollment.

	Routine management (n=192)	Intensive management (n=188)	P
Male (n,%)	117 (60.9)	112 (59.9)	0.428
Age	54.7±11.2	53.9±10.9	0.232
Smoking (n,%)	65 (33.9)	67 (35.8)	0.183
History of diabetes (n,%)	63 (32.8)	58 (31.0)	0.216
History of ischemic stroke (n,%)	42 (21.9)	48 (25.7)	0.147
TT genotype of the MTHFR gene (n,%)	74 (38.5)	75 (40.1)	0.277
BMI (kg/m2)	24.57±4.93	24.71±4.86	0.241
TC (mmol/L)	4.92±1.02	4.94±1.06	0.563
TG (mmol/L)	2.53±0.82	2.36±1.47	0.608
HDL-C (mmol/L)	1.05±0.38	1.03±0.40	0.159
LDL-C (mmol/L)	2.29±0.73	2.31±0.80	0.328
FBG (mmol/L)	5.28±1.22	5.33±1.26	0.097
SBP (mmHg)	154.28±12.22	154.79±11.25	0.835
DBP (mmHg)	88.36±11.55	89.71±11.04	0.295
Hcy (μmol/l)	19.93±7.31	20.34±5.85	0.102
History of hyperlipidemia (n,%)	161 (83.9)	157 (83.5)	0.262
Number of patients using statins before inclusion (n,%)	161 (83.9)	157 (83.5)	0.262

MTHFR – methylenetetrahydrofolate reductase; BMI – body mass index; TC – total cholesterol; TG – triglycerides; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; FBG – fasting blood glucose; SBP – systolic blood pressure; DBP – diastolic blood pressure; Hcy – homocysteine.

independent-samples *t* test. If non-normally distributed, data were expressed as median (range) and analyzed using the Mann-Whitney U test. Categorical data were presented as frequencies and compared using the Fisher's exact test. Two-tailed P-values <0.05 were considered statistically significant.

Results

Demographic information

Four hundred patients were enrolled; 3 reported an age that was incorrect after ID card validation, making them ineligible, and 10, 5, and 2 were excluded because of poor compliance, lack of carotid plaque data, and informed consent withdrawal, respectively. Finally, 380 patients were analyzed, including 229 men and 151 women, aged between 40 and 75 years (54.68±11.28 years). There were 188 and 192 patients assigned to the intensive and routine management groups, respectively (Figure 1C). No significant differences between groups were found regarding age, BMI, blood glucose, blood cholesterol, baseline blood pressure, and serum Hcy (Table 1).

Intensive blood pressure control results in reduced blood pressure

The BP targets were achieved in both groups from the second month of treatment initiation. As per management protocol, blood pressure in the intensive group was significantly lower than in the routine group. Blood pressure indexes in both groups are summarized in Table 2 and Figure 2. By the end of follow-up, 11 patients in each group were lost to follow-up. There were no significant differences in blood lipids from baseline to 12 months in the 2 groups.

Intensive blood pressure control improves the parameters of carotid atherosclerosis

The carotid plaque areas and Crouse scores were significantly lower in the intensive management group compared with

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Table 2. Blood pressure indexes in the 2 treatment groups.

	Routine management (n=192)	P (*vs.* baseline)	Intensive management (n=188)	P (*vs.* routine)	P (*vs.* baseline)
n at 1 month	190		186		
SBP at 1 month	124.72±9.27	<0.001	119.42±11.33	0.052	<0.001
n at 2 months	190		185		
SBP at 2 months	128.64±8.71	<0.001	106.37±9.64	0.035	<0.001
n at 3 months	189		185		
SBP at 3 months	129.83±9.38	<0.001	108.59±11.38	0.041	<0.001
n at 6 months	188		183		
SBP at 6 months	128.85±7.35	<0.001	111.37±8.26	0.048	<0.001
n at 12 months	181		177		
SBP at 12 months	132.78±10.43	<0.001	108.93±10.11	0.026	<0.001
Number of anti-hypertensive drugs at 12 months	1.8±0.6	NA	2.3±0.7	0.045	NA
BMI (kg/m^2)*	23.67±4.89	0.054	23.55±4.83	0.195	0.056
TC (mmol/L)*	4.83±0.92	0.147	4.83±1.06	0.557	0.155
TG (mmol/L)*	2.54±0.77	0.327	2.33±1.62	0.598	0.361
HDL-C (mmol/L)*	1.05±0.42	0.589	1.05±0.36	0.221	0.432
LDL-C (mmol/L)*	2.34±0.86	0.386	2.29±0.92	0.297	0.377
FBG (mmol/L)*	5.22±1.38	0.418	5.34±1.31	0.164	0.387
Hcy (μmol/l)*	8.29±2.22	0.024	8.43±2.38	0.231	0.033

SBP – systolic blood pressure; BMI – body mass index; TC – total cholesterol; TG – triglycerides; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; FBG – fasting blood glucose; Hcy – homocysteine. By the end of follow-up, 11 patients in each group were lost to follow-up. * At 12 months.

controls after 12 months of treatment (both P<0.05). There were no significant differences regarding IMT and IMT/D between the 2 groups (all P>0.05). Furthermore, compared with the control group, intensive treatment resulted in significantly lower Vs/Vd, PI, and RI (all P<0.05). Detailed data are provided in Table 3. No correlation could be found between changes in BP and changes in plaque score or hemodynamic indexes (data not shown).

Correlations

Blood pressure change (12 months – baseline) was positively correlated with changes (12 months – baseline) in plaque area (r=0.702, P=0.041), plaque score (r=0.773, P=0.028), Vs/Vd (r=0.751, P=0.039), PI (r=0.797, P=0.015), and RI (r=0.824, P=0.011). To control for potential confounders, a multivariate analysis was performed. The change (12 months – baseline) in plaque area was set as the dependent variable. Age, sex, changes in blood pressure (12 months – baseline), blood lipids, glucose, and Hcy were set as independent variable. The results indicated that the changes in blood pressure (12 months – baseline) (β=0.124, 95% confidence interval: 0.042–0.288, P=0.026), and age (β=0.253, 95% confidence interval: 0.195–0.371, P=0.012) were independently associated with the changes in plaque area (12 months – baseline) (R^2=0.569).

Occurrence of cerebrovascular events and adverse effects

Six (3.12%) and 5 (2.67%) patients had stroke after treatment for 12 months in the intensive and standard treatment groups, respectively (P=0.246). The main adverse effects were hypotension and dizziness, which were slightly higher in the intensive group compared with controls (Table 4).

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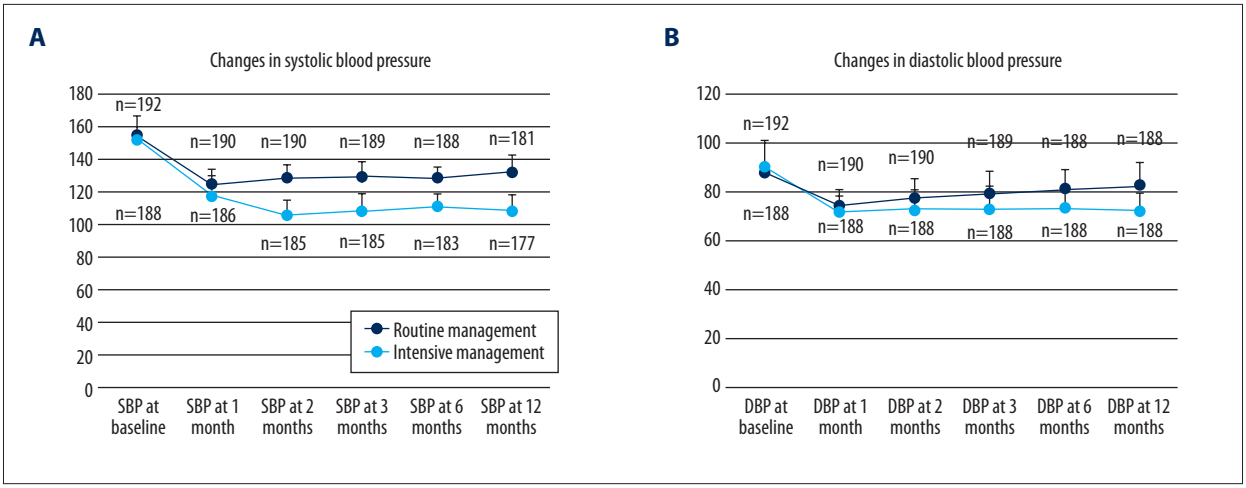

Figure 2. Changes in systolic (SBP; **A**) and diastolic (DBP; **B**) blood pressure in the 2 groups during the 12-month treatment period.

Table 3. Carotid atherosclerosis parameters in the 2 groups.

	Routine management (n=192)		Intensive management (n=188)		P at baseline	P at 12 months
	Baseline	12 months	Baseline	12 months		
Plaque area (mm²)	26.03±3.48	24.56±3.14	26.17±3.51	18.41±2.13	0.482	0.038
Plaque score (mm)	3.31±0.64	2.45±0.47	3.28±0.63	1.75±0.52	0.217	0.023
IMT (mm)	1.13±0.10	0.99±0.14	1.14±0.13	0.92±0.19	0.231	0.062
IMT/D	16.71±3.96	15.53±4.87	16.88±4.05	11.47±2.30	0.362	0.089
Vd (cm/s)	76.38±6.42	92.31±9.72	79.74±6.94	107.53±8.42	0.225	0.056
Vs/Vd	2.06±0.25	1.88±0.18	2.01±0.18	1.68±0.11	0.126	0.031
PI	0.88±0.17	0.69±0.12	0.91±0.14	0.51±0.03	0.273	0.017
RI	0.79±0.06	0.52±0.01	0.74±0.05	0.30±0.03	0.328	0.008

IMT – intima-media thickness; D – carotid diameter; Vd – end-diastolic velocity; Vs – peak systolic velocity; PI – pulsatility index; RI – resistance index.

Table 4. Occurrence of adverse events in the 2 groups.

	Routine management (n=192)	Intensive management (n=188)	P
Adverse effects	19 (9.89%)	25 (13.36)	0.075
Withdrawn from trial	7/192	10/188	0.430
Hypotension	3 (1.56%)	5 (2.67%)	0.020
Bradycardia	4 (2.01%)	4 (2.13%)	0.281
Electrolyte disorder	4 (2.01%)	5 (2.67%)	0.094
Dizziness	16 (8.33%)	20 (10.69%)	0.041
Abnormal renal function	3 (1.56%)	2 (1.06%)	0.194

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Discussion

The results of the present study strongly suggest that intensive hypertension management resulted in significantly lower carotid plaque areas and scores compared with routine management in patients with H-type hypertension and high risk of stroke. Vs/Vd, PI, and RI were significantly lower after intensive management compared with the control group. No significant difference between the 2 groups was found in terms of cerebrovascular events. The major adverse effects were hypotension and dizziness, with incidence rates relatively higher in the intensive treatment group. No significant differences were observed between the 2 groups regarding bradycardia, electrolyte disturbance, renal dysfunction, and medication withdrawal occurrences. Nevertheless, the patients in the intensive group received a more anti-hypertension drugs compared with the control group because the BP targets were lower for the intensive management scheme than for the standard management scheme.

H-type hypertension refers to hypertension with hyperhomocysteinemia (Hcy ≥10 μmol/L) and is in itself an important risk factor for cardiovascular events and stroke [22]. Given the particularly high rate of the MTHFR C677T mutation in Hcy metabolism in the Chinese population and in relation to the Chinese diet, the incidence of H-type hypertension is significantly higher in China compared with other counties [3,23,24]. Previous studies showed that awareness, treatment, and control rates of hypertension in China were low [4]. This results in significantly higher stroke incidence and mortality compared with global averages, although coronary disease incidence and related mortality are lower compared with other countries [3,23,24]. The Third National Survey on Death Causes indicated that cerebrovascular diseases have become the primary cause of death in China [25]. Meanwhile, the incidence of ischemic stroke steadily increases by 8.7% annually [14]. Therefore, the key point in the prevention and treatment of cerebrovascular disease is stroke prevention. In other words, it is very important to provide primary stroke prevention in H-type hypertension in China, and physicians must thus effectively control blood pressure for patients.

Currently, the target blood pressure for H-type hypertension remains unclear due to the lack of evidence from large randomized trials. Nevertheless, blood pressure control in these patients is essential since H-type hypertension has been shown to be an independent factor for asymptomatic extracranial artery stenosis and primary and recurrent ischemic strokes [1,23,26]. Recent evidence-based guidelines for the management of high blood pressure in adults [9,10] recommend a loose goal for blood pressure control, while emphasizing the need for individualized blood pressure targets in different cohorts. The ACCORD study demonstrated that the annual stroke incidence could be significantly reduced by intensive blood pressure control (0.32% *vs.* 0.53%; risk ratio of 0.59, 95%CI 0.39-0.89) [11]. A 2012 meta-analysis by McBrien et al. [12], assessing 7312 hypertensive patients with type II diabetes, compared stroke incidences with targeted blood pressures of ≤130/80 mmHg and ≤140–160/85–100 mmHg, and found that intensive blood pressure control could significantly reduce the risk of stroke by 35%. The effect of intensive blood pressure control on cerebrovascular blood flow velocity in type II diabetes patients was evaluated by Kim et al. [13]; after intensive blood pressure control, a transient decrease of cerebral blood flow velocity was only found in patients without microvascular complications, suggesting that for type II diabetes patients, intensive blood pressure control should be initiated at the early stage of hypertension when the automatic regulatory function of the brain is still sufficient to counteract the effect of decreased perfusion [13]. The recently released SPRINT study indicated that intensive blood pressure control reduces cardiovascular risk by 25% [14]. Together, these findings suggest that intensive blood pressure control could benefit patients with specific types of hypertension. In this study, the carotid plaque area and score were significantly lower in patients receiving intensive management compared with those receiving routine management, as supported by the previous study described above, suggesting that H-type hypertension patients with high risk of stroke could benefit from intensive blood pressure control.

It was reported that carotid atherosclerosis plays an important role in cerebral infarction, with extracranial atherosclerotic plaque representing the major cause of stroke [16,27–29]. Indeed, increased vascular intima-media thickness was revealed as a phenotype of atherosclerosis at an early stage; therefore, this parameter was used in the present study for the early diagnosis of stroke [30]. Though IMT is broadly used in clinical practice, it has many limitations. First of all, atherosclerosis is an endothelial disease, and acute cerebral infarction is caused by rupture of an unstable plaque [27–29], but ultrasound scanning for IMT poorly differentiates intima-media from endothelial thicknesses, and stable from unstable plaques; alteration in IMT could be due to medial hypertrophy or atherosclerosis. Secondly, IMT and plaque response are different aspects and stages of atherosclerotic disease [31]. Accumulating evidence indicates that the properties and amount of carotid plaques are associated with cerebral infarction and severity; in addition, plaque area and score are more associated with cerebrovascular events than with IMT [32–35]. In the present study, although no significant improvement of IMT was found after intensive management *vs.* routine management, plaque score and area were both significantly improved, indicating that intensive blood pressure control could benefit patients with certain types of hypertension. Surprisingly, LDL-C did not change, in spite of treatment with atorvastatin 20 mg/d for 12 months.

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In fact, many patients were already taking a statin before the study, and the patients were all given the same dose of atorvastatin in order to minimize this bias during the study. Hence, in the present study, the major effect on carotid morphology was probably related to the larger BP drop in the intensive care group compared with the control group, rather than to improvement in other parameters that may affect the arterial wall.

Cerebral blood supply disorder is the main cause and an important pathogenesis factor of cerebral arteriosclerosis. The middle cerebral artery is a straight blood vessel with rare congenital variation and could be used to predict the risk of cerebral vascular disease induced by atherosclerosis. PI is an index reflecting cerebral vascular compliance and elasticity, while RI describes cerebral vascular resistance, both of which could be used as sensitive indexes for the diagnosis and prognosis of ischemic cerebrovascular disease [36]. In this study, Vs/Vd, PI, and RI in the intensive management group were significantly lower compared with the control group, indicating that intensive treatment can alleviate cerebrovascular disease.

A limitation of this study was its small sample size. In addition, there was no significant difference between the 2 groups regarding the occurrence of stroke, but the follow-up was short and stroke pathogenesis is an ongoing process over many years. Nevertheless, carotid plaque index improvements were better with intensive than routine management, suggesting potential long-term benefits, which will have to be confirmed. We cannot exclude that folic acid and atorvastatin had stronger effects on stroke incidence than blood pressure management. This study only examined Chinese patients with H-type hypertension; therefore, its generalizability is limited. Finally, and most importantly, despite predefined management algorithms, anti-hypertensive treatment was achieved by arbitrary selection of various drug classes without a controlled regimen, and this may have affected the overall results. Additional studies with different treatment strategies could provide some more definitive results.

Conclusions

Intensive blood pressure management can benefit patients with H-type hypertension and high risk of stroke. Although the subjects of this study were patients with H-type hypertension, the results of this study are similar to those of previous reports in patients with hypertension without hyperhomocysteinemia. Nevertheless, well-designed clinical trials with a larger study population are required to confirm these findings.

Conflict of interest

None.

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