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High Blood Pressure Increases the Risk of Poor Outcome at Discharge and 12-month Follow-up in Patients with Symptomatic Intracranial Large Artery Stenosis and Occlusions: Subgroup analysis of the CICAS Study

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SUMMARY

Aims: The purpose of this study was to discuss the relationship between blood pressure and prognosis of patients with symptomatic intracranial arterial stenosis. **Methods:** Data on 2426 patients with symptomatic intracranial large artery stenosis and occlusion who participated in the Chinese Intracranial Atherosclerosis (CICAS) study were analyzed. According to the JNC 7 criteria, blood pressure of all patients was classified into one of the four subgroups: normal, prehypertension, hypertension stage I, and hypertension stage II. Poor outcomes were defined as death and functional dependency (mRS 3-5) at discharge or at 1 year. **Results:** For patients with intracranial stenosis of 70% to 99%, the rate of poor outcome at discharge was 19.3%, 23.5%, 26.8%, and 39.8% ($P = 0.001$) for each blood pressure subgroup. For patients with intracranial large artery occlusion, the rates were 17.6%, 22.1%, 29.5%, and 49.8%, respectively ($P < 0.0001$). The rate of poor outcome at 12-month follow-up was 12.6%, 15.3%, 28.5%, and 27.9% ($P = 0.0038$) in patients with stenosis of 70% to 99% for each blood pressure subgroup and 11.6%, 21.5%, 23.9%, 35.1% ($P < 0.0001$) in patients with occlusion. **Conclusions:** For patients with severe intracranial arterial stenosis or occlusion, higher hypertension stages are associated with an increased risk of poor outcome at discharge and 12-month follow-up.

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The first two authors contributed equally to this work;

Introduction

Stroke is one of the leading causes of death in China and has a significant impact on healthcare expenditures and Chinese economy [1]. There are more patients suffering from intracranial atherosclerotic diseases in China compared with Western countries [2,3]. Finding from a recent multicenter study of the prevalence and outcomes of intracranial large artery atherosclerosis among patients with stroke and transient ischemic attack in China (the Chinese Intracranial Atherosclerosis (CICAS) study) showed that the prevalence of intracranial stenosis was up to 46.6% [4].

Hypertension is an important predictor for stroke outcome; data from CNSR prompted that admission systolic blood pressure was associated with poor outcomes at 3 and 12 months in intracerebral hemorrhage patients [5]. However, the relationship between blood pressure and stroke prognosis was still controversial [6,7]. The effect of blood pressure on the prognosis varies depending on the different stroke subtypes [8]. To date, a few studies have investigated the relationship between the blood pressure and prognosis of symptomatic intracranial artery stenosis. Evidence from WASID study indicates that higher blood pressure was associated with greater risk of ischemic stroke and stroke in the territory of the stenotic vessel [9]. Although select bias would not be avoided in a drug clinical trial. Another small sample study shows that patients with higher blood pressure on admission were associated with an increased risk of death or disability in those patients [6]. Therefore, antihypertensive therapies should have positive blood pressure-independent effects on stroke risk [10]. As blood pressure could be affected by multiple factors, this conclusion is not generalizable. In addition, fewer researches were carried out to study the relationship between blood pressure and stroke functional outcome in patients with different degree of stenosis.

According to JNC 7 [11], patients were classified into four subgroups by level of blood pressure. The aim of our study was to analyze the relationship between blood pressure and stroke prognosis in patients with various severity of stenosis. A discussion was presented on how blood pressure affects the prognosis of patients with symptomatic intracranial artery stenosis or occlusion.

Materials and Methods

Patient Population and Study Design

The CICAS study is a prospective and hospital-based multicenter study at 22 sites in China. In total, 2864 patients were enrolled in CICAS study, of which 307 had no blood pressure information and 141 had extracranial lesions only, so that they were excluded from the current study. Details of the study design have been published elsewhere [4]. All patients underwent three-dimensional time-of-flight MRA. Extracranial carotid vessels were examined by duplex color Doppler ultrasound or contrast-enhanced MRA. According to the severity of stenosis, patients were categorized into four groups: <50% or no stenosis, 50% to 69% stenosis, 70% to 99% stenosis, and occlusion. In accordance with the JNC 7 classification by level of blood pressure, patients was classified into prehypertension (ranging from 120 to 139 mmHg systolic and/or 80 to 89 mmHg diastolic), normal (<120/80 mmHg), stage I hypertension (ranging from 140 to 159 mmHg systolic and/or 90 to 99 mmHg diastolic), and stage II hypertension (≥160 mmHg systolic and/or ≥100 mmHg diastolic) [11]. During hospitalization, professional nurses made two or more measurements at different time of morning, noon, or afternoon every day. If the patients could not sit, the BP would be measured in the decubitus position. The diagnosis was determined by trained physicians according to the overall level of BP in hospital and past history.

Follow-up and Endpoints

Patients were contacted via telephone by trained research personnel from Beijing Tiantan Hospital and Hong Kong Prince of Wales Hospital using standard scripts at discharge and at 12 months after stroke onset. Each case fatality was either confirmed on a death certificate from the local citizen registry or from the attended hospital. Endpoints were disability and any cause of death. The modified Rankin Scale (mRS) scores of 3 to 5 were considered as disabled.

Statistical Analyses

All analyses were carried out with SAS software version 9.1.3 (SAS Institute, Cary, NC, USA). Continuous variables were summarized as median (interquartile range [IQR]) or (mean ± SD). Categorical variables such as male sex, vascular risk factors, and classification of blood pressure were presented as percentages. Independent samples of *t*-test or Wilcoxon's test were used for comparison of continuous variables, and chi-squared test or Fisher's exact test was used for comparison of categorical variables. Odds ratios (ORs) and their 95% confidence intervals (CI) for the degree of ICAS (intracranial atherosclerosis) associated with various blood pressure subgroups were calculated using logistic regression analysis. All tests were 2-sided, with a significance level fixed at 5%.

Results

Baseline Characteristics

A cohort of 2426 consecutive patients was analyzed in the study. Of total, 1645(67.8%)patients were male. The mean age on admission for index stroke was 61.6 (±11.3) years. The percentage of diabetes mellitus, hyperlipidemia, current smoker, heavy alcohol use, hyperhomocysteinemia, history of previous stroke/TIA, Heart disease, body Mass Index, NIH Stroke Scale at admission, blood creatinine, statins, antiplatelet therapy, blood pressure-lowering therapy, multiple ICAS, type of vascular lesion, distribution of ICAS, and pattern of infarct were significantly different among subgroups of different hypertension stages by JNC 7, while others had nonsignificant difference. The clinical features of the participants have been summarized in Table 1.

Blood pressure and poor outcome

The rate of poor outcome at discharge was found to be increased with higher category of blood pressures. Among patients with stenosis of <50%, the rate of poor outcome at discharge was 13.06%, 14.63%, 34.48%, and 40.80% ($P < 0.0001$) in each blood pressure subgroup (from normal, to prehypertension, to hypertension stage I, and to hypertension stage II). Among patients with 50% to 69% stenosis, the rates were 25.0%, 27.3%, 30.8%, and 43.0%, respectively ($P = 0.4508$). In patients with 70% to 99% stenosis, the rate of poor outcome at discharge was 19.3%, 23.5%, 26.7%, and 39.7% ($P = 0.0010$). Among patients with occlusion the rate was 17.6%, 22.1%,

Table 1 Baseline characteristics of 2426 patients by the classification of JNC 7 hypertension stage

Characteristics	Total	Normal	Prehypertension	Hypertension stage I	Hypertension stage II	*P* value
Male sex	1645	333 (71.9)	72 (75.0)	276 (67.0)	964 (66.3)	0.0550
Age[a], mean, (SD), year	61.6 ± 11.3	58.8 ± 12.5	58.8 ± 12.8	62.9 ± 10.3	62.3 ± 10.9	<0.0001
Diabetes mellitus	862	115 (24.8)	27 (28.1)	144 (35.0)	576 (39.6)	<0.0001
Hyperlipidemia	1862	328 (70.8)	75 (78.1)	305 (74.0)	1154 (79.3)	0.0010
Family history of stroke	254	39 (8.4)	12 (12.5)	38 (9.2)	165 (11.3)	0.2261
Current smoker	898	198 (42.8)	48 (50.0)	147 (35.7)	505 (34.7)	0.0007
Heavy drinker	124	26 (5.6)	10 (10.4)	12 (2.9)	76 (5.2)	0.0189
Hyperhomocysteinemia	680	98 (21.2)	40 (41.7)	109 (26.5)	433 (29.8)	<0.0001
History of previous stroke/TIA	1703	261 (56.4)	59 (61.5)	290 (70.4)	1093 (75.1)	<0.0001
History of hemorrhage stroke	45	9 (1.9)	1 (1.0)	9 (2.2)	26 (1.8)	0.8845
Heart disease	210	23 (5.0)	9 (9.4)	38 (9.2)	140 (9.6)	0.0193
Peripheral vascular disease	20	2 (0.4)	3 (3.1)	3 (0.7)	12 (0.8)	0.0678
Body mass index[a]	24.6 ± 3.2	24.0 ± 3.3	24.6 ± 3.0	24.5 ± 3.0	24.8 ± 3.2	<0.0001
NIH Stroke Scale at admission[b]	4.0 (1.0–7.0)	3.0 (1.0–6.0)	3.0 (1.0–7.0)	4.0 (2.0–7.0)	4.0 (2.0–7.0)	0.0173
Blood creatinine[a]	81.3 ± 37.1	76.0 ± 17.5	75.5 ± 17.1	81.1 ± 37.7	83.4 ± 33.6	0.0002
Antiplatelet therapy	2274	424 (91.6)	87 (90.6)	371 (90.1)	1392 (95.7)	<0.0001
Statins	1867	328 (70.8)	76 (79.2)	310 (75.2)	1153 (79.2)	0.0018
Blood pressure-lowering therapy	1275	22 (4.8)	22 (22.9)	216 (52.4)	1015 (69.8)	<0.0001
Type of vascular lesion						
None	1230	268 (57.9)	44 (45.8)	213 (51.7)	705 (48.5)	0.0262
Intracranial only	949	155 (33.5)	39 (40.6)	157 (38.1)	598 (41.1)	
Intra- and extracranial	247	40 (8.6)	13 (13.5)	42 (10.2)	152 (10.5)	
Multiple ICAS	519	63 (13.6)	20 (10.8)	70 (17.0)	366 (25.2)	<0.0001
Distribution of ICAS						
None	1230	268 (57.9)	44 (45.8)	213 (51.7)	705 (48.5)	<0.0001
Anterior	596	124 (26.8)	38 (39.6)	96 (23.3)	338 (23.2)	
Posterior	304	39 (8.4)	4 (4.2)	67 (16.3)	194 (13.3)	
Anterior and posterior	296	32 (6.9)	10 (10.4)	36 (8.7)	218 (15.0)	
Severity of ICAS						
None or <50%	1230	268 (57.9)	44 (45.8)	213 (51.7)	705 (48.5)	0.0056
50–69%	304	41 (8.9)	11 (11.5)	53 (12.9)	199 (13.7)	
70–99%	221	29 (6.3)	13 (13.5)	30 (7.3)	149 (10.2)	
100%	671	125 (27.0)	28 (29.2)	116 (28.2)	402 (27.6)	
Multiple infarctions	235	45 (13.7)	10 (13.9)	37 (12.0)	143 (12.8)	0.9224
Pattern of infarct						
No infarct	537	124 (27.4)	20 (21.7)	96 (23.8)	297 (21.0)	<0.0001
Cortical	93	20 (4.4)	5 (5.4)	19 (4.7)	49 (3.5)	
Subcortical	945	158 (35.0)	39 (42.4)	164 (40.6)	584 (41.3)	
Mixed cortical and subcortical	331	91 (20.1)	16 (17.4)	50 (12.4)	174 (12.3)	
Infratentorial	418	52 (11.5)	12 (13.04)	71 (17.6)	283 (20.0)	
Supra- and infratentorial	37	7 (1.6)	0 (0)	4 (1.0)	26 (1.8)	
White matter changes	997	117 (25.3)	27 (28.1)	170 (41.3)	683 (47.0)	<0.0001
Complete circle of Willis	117	30 (6.5)	5 (5.2)	17 (4.1)	65 (4.4)	0.3036
Border zone	206	47 (10.2)	16 (16.7)	29 (7.0)	114 (7.8)	0.0080

ICAS indicates intracranial atherosclerosis. [a]Continuous variable with normal distribution was expressed as mean ± SD; other values are expressed as n (%). [b]NIH Stroke Scale with abnormal distribution was expressed as medians with IQR in parentheses.

29.5%, and 49.8% ($P < 0.0001$). The same trend was observed at 12-month poor outcome. In patients with stenosis <50%, the rate of poor outcome at discharge were 6.6%, 7.5%, 17.8%, and 28.2% ($P < 0.0001$). Among patients with 50% to 69% stenosis the rate was 16.6%, 27.2%, 23.0%, and 21.4% ($P = 0.8592$). Among patients with 70% to 99% stenosis, the rate of poor outcome at 12-month was 12.6%, 15.3%, 28.5%, and 27.9% ($P = 0.0038$). In patients with occlusion the rate was 11.6%, 21.5%, 23.9%, and 35.1% ($P < 0.0001$). The trend of poor outcome has been shown in Figures 1 and 2.

The degree of ICAS associated with various blood pressure subgroups was calculated using logistic regression analysis adjusted on age, hyperhomocysteinemia, body mass index, NIHSS at admission, distribution of ICAS, border-zone infarction, degree of stenosis, antiplatelet therapy, statins, blood pressure-lowering therapy. The adjusted *P* values were all >0.05. (Table 2)

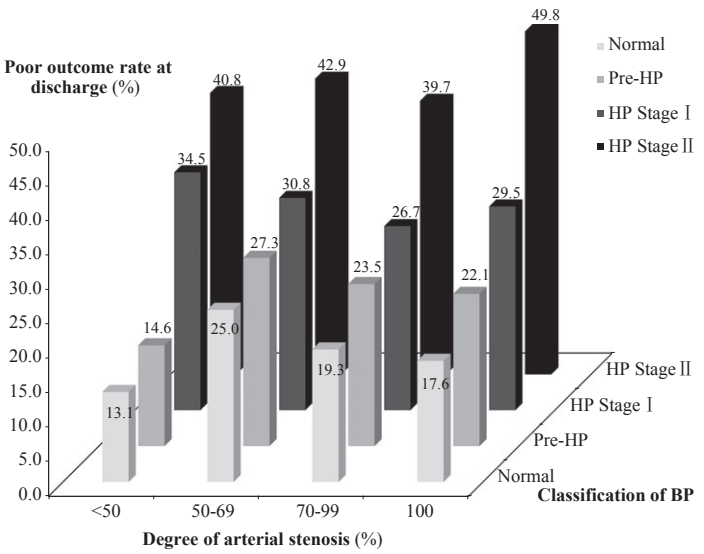

Figure 1 Trends of poor outcome rate at discharge by the degree of stenosis and categories for blood pressure. Number above each block indicates the rate of poor outcome. HP: hypertension; BP: blood pressure.

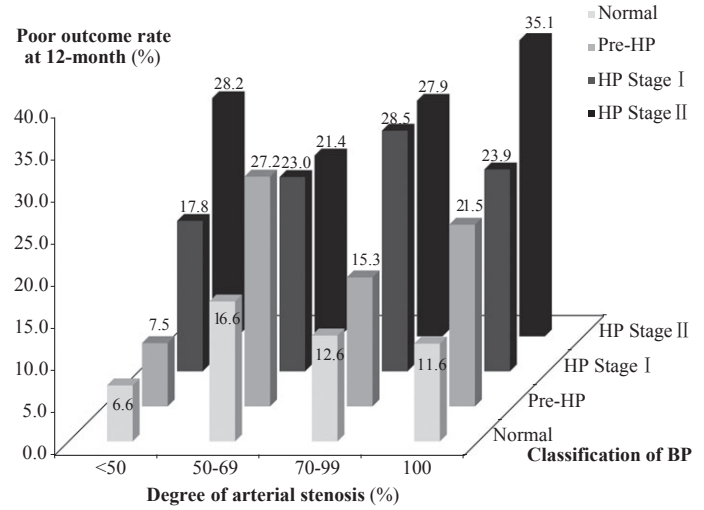

Figure 2 Trends of poor outcome rate at 12-month follow-up by the degree of stenosis and categories for blood pressure. Number above each block indicates the rate of poor outcome. HP: hypertension; BP: blood pressure.

Discussion

Intracranial large arterial stenosis or occlusion was very common in Chinese ischemic stroke patients [4]. These patients usually had more severe strokes at admission, stayed longer in hospitals and had high risk of recurring strokes, up to 25–30% in 2 years after stroke [12–14]. Only a few large, multicenter randomized trials evaluating stroke-preventive therapies for this special population have been performed. Hypertension was an important modifiable risk factor. In SAMMPRIS trial, achievement of SBP <140 mmHg was recommended for patients with severe stenosis (70%–99%) of a major intracranial artery [15].

Our study provided the data supporting the need to control blood pressure in patients with ICAS. The relationship between blood pressure and functional outcomes in acute ischemic stroke patients with ICAS or occlusion in a hospitalized Chinese population was investigated. The results showed that the rate of poor outcome at discharge and 12-month follow-up increased with increase of hypertension stage by JNC 7 criteria in patients with severe stenosis and occlusion. The highest rate of poor outcome was observed among patients with intracranial arterial occlusion and stage II hypertension. However, the hypertension stage was not an independent predictor of poor outcome at discharge or 12-month follow-up. In this study, patients with higher hypertension stages were older and likely to have multiple vascular risk factors and higher percentage of multiple intracranial artery lesions, white matter changes, and more cardiac and renal complications. These comorbidities likely contributed to the poor outcome in these patients.

In subanalysis of WASID trial by Turan et al. [9], increased risk of ischemic stroke and stroke in the territory of the stenotic vessel was found among 567 patients with symptomatic 50% to 99% stenosis of a major intracranial artery and higher BP, even though the data were not grouped together according to the severity of ste-

Table 2 Odds ratios and 95% CIs according to categories of JNC 7 for poor outcome at discharge and 12-month follow-up

	Unadjusted				Adjusted[a]			
Classification of BP	Poor outcome at discharge OR (95% CI)	*P*	Poor outcome at 12-month follow-up OR (95% CI)	*P*	Poor outcome at discharge OR (95%CI)	*P*	Poor outcome at 12-month follow-up OR (95% CI)	*P*
50–69%								
Normal								
Prehypertension	2.19 (0.45–10.67)	0.57	4.62 (0.79–27.23)	0.24	4.45 (0.38–51.98)	0.23	–	0.94
Hypertension stage I	1.90 (0.65–5.52)	0.62	2.24 (0.55–9.06)	0.82	1.91 (0.26–14.11)	0.53	–	0.94
Hypertension stage II	1.66 (0.65–4.19)	0.93	3.39 (1.00–11.56)	0.23	1.70 (0.31–9.42)	0.54	–	0.94
70–99%								
Normal								
Prehypertension	0.84 (0.21–3.44)	0.96	1.38 (0.28–6.92)	0.99	3.71 (0.33–41.89)	0.29	4.53 (0.53–38.36)	0.17
Hypertension stage I	0.69 (0.23–2.11)	0.62	1.84 (0.52–6.54)	0.45	0.14 (0.01–1.78)	0.13	1.60 (0.24–10.56)	0.63
Hypertension stage II	0.80 (0.34–1.85)	0.88	1.45 (0.51–4.10)	0.87	0.74 (0.11–5.29)	0.77	3.30 (0.60–18.23)	0.17
100%								
Normal								
Prehypertension	1.09 (0.48–2.49)	0.96	0.69 (0.26–1.87)	0.32	1.36 (0.27–6.94)	0.71	0.86 (0.20–3.71)	0.84
Hypertension stage I	0.95 (0.57–1.60)	0.41	0.99 (0.55–1.76)	0.99	0.89 (0.35–2.22)	0.80	0.95 (0.42–2.17)	0.91
Hypertension stage II	1.44 (0.96–2.16)	0.06	1.38 (0.87–2.17)	0.04	1.84 (0.87–3.89)	0.11	1.36 (0.69–2.69)	0.38

The odds ratios (ORs) and probability values are for comparisons between the lowest blood pressure category and each of the higher blood pressure categories. CI was the abbreviation for confidence intervals. [a]Adjusted by age, hyperhomocysteinemia, body mass index, NIHSS at admission, distribution of ICAS, border-zone infarction, degree of stenosis, antiplatelet therapy, statins, blood pressure-lowering therapy.

nosis. In our study, there was no significant correlation between poor outcome and hypertension stage in patients with stenosis of 50–69%. Furthermore, WASID study measured the blood pressure at chronic stage of stroke that included the patients with TIA or nonsevere stroke within 90 days prior to randomization. The relationship of BP and outcome in patients at acute or subacute stage of stroke with ICAS remained uncertain. Zilonghao et al. [6] carried out a similar study of 215 stroke patients within 2 weeks of admission. They observed that higher blood pressure on admission was associated with an increased risk of death or disability among patients with symptomatic ICAS (70%–99%) or occlusion.

According to the pathophysiology, ischemic stroke is due to the abrupt loss of cerebral blood flow to a portion of the brain [8]. Clinic deficits in acute ischemic stroke are caused by both the infracted core and ischemic penumbra. The primary aim of stroke care is to preserve the penumbra, which means optimizing BP and cerebral blood flow. Some studies found a U-shaped relationship between BP and outcome after ischemic stroke exists [16,17]. As the optimal range of BP for the penumbra is small, too much of variation may cause further ischemic damage. The optimal range of BP is unknown and may differ among individuals with different stroke subtypes. This theory had been confirmed by studies from symptomatic carotid artery disease. Rothwell PM et al. [18] found that the risk of stroke increases with blood pressure in the great majority of patients with symptomatic carotid artery disease, but the relationship was less steep than in other patients with TIA or stroke. The relationship was unaffected by unilateral carotid occlusion alone but was inverted among patients with bilateral >70% carotid stenosis, suggesting that decreasing blood pressure dramatically may not be recommended in these patients.

The current study has several limitations. First, variability and instability in blood pressure had an important role in the progression of organ damage and triggering of vascular events [19]. This study did not take these factors into account. Further research is needed to define the relationship between variability in blood pressure and outcome of patients with intracranial artery stenosis. Second, classification of BP according to JNC 7 does not define very low or high blood pressure. Therefore, our study reflected certain ranges of BP and the outcome. Thirdly, it had been observed that the blood pressure in acute ischemic stroke patients would decline spontaneously within the first week after the onset. In our study, the trained physicians gave the diagnosis at discharge according to the blood pressure of each day during hospitalization and history of hypertension. Further studies should be launched on continuous monitoring of blood pressure after stroke, which may more valuable for prediction.

In conclusion, the rate of poor outcome at discharge and 12-month follow-up was increased in patients with elevated hypertension stages defined by JNC 7 and intracranial arterial stenosis of 70–99% or occlusion. The highest rate of poor outcome was observed among patients with occlusion plus stage II hypertension. Patients with higher hypertension stages are older with more vascular risk factors and higher percentage of multiple intracranial arterial lesions, white matter changes, and cardiac and renal complications. Our findings support the need to lower blood pressure in stroke patients with severe ICAS and/or occlusions.

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Conflict of Interest

The authors declare no conflict of interest.

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