Relationship of Blood Pressure, Antihypertensive Therapy, and Outcome in Ischemic Stroke Treated With Intravenous Thrombolysis

Retrospective Analysis From Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR)

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Background and Purpose—The optimal management of blood pressure (BP) in acute stroke remains unclear. For ischemic stroke treated with intravenous thrombolysis, current guidelines suggest pharmacological intervention if systolic BP exceeds 180 mm Hg. We determined retrospectively the association of BP and antihypertensive therapy with clinical outcomes after stroke thrombolysis.

Methods—The SITS thrombolysis register prospectively recorded 11 080 treatments from 2002 to 2006. BP values were recorded at baseline, 2 hours, and 24 hours after thrombolysis. Outcomes were symptomatic (National Institutes of Health Stroke Scale score deterioration ≥4) intracerebral hemorrhage Type 2, mortality, and independence at (modified Rankin Score 0 to 2) 3 months. Patients were categorized by history of hypertension and antihypertensive therapy within 7 days after thrombolysis: Group 1, hypertensive treated with antihypertensives (n=5612); Group 2, hypertensive withholding antihypertensives (n=1573); Group 3, without history of hypertension treated with antihypertensives (n=995); and Group 4, without history of hypertension not treated with antihypertensives (n=2632). For 268 (2.4%) patients, these data were missing. Average systolic BP 2 to 24 hours after thrombolysis was categorized by 10-mm Hg intervals with 100 to 140 used as a reference.

Results—In multivariable analysis, high systolic BP 2 to 24 hours after thrombolysis as a continuous variable was associated with worse outcome ($P<0.001$) and as a categorical variable had a linear association with symptomatic hemorrhage and a U-shaped association with mortality and independence with systolic BP 141 to 150 mm Hg associated with most favorable outcomes. OR (95% CI) from multivariable analysis showed no difference in symptomatic hemorrhage (1.09 [0.83 to 1.51]; $P=0.58$) and independence (1.03 [0.93 to 1.10]; $P=0.80$) but lower mortality (0.82 [0.73 to 0.92]; $P=0.0007$) for Group 1 compared with Group 4. Group 2 had a higher symptomatic hemorrhage (1.86 [1.34 to 2.68]; $P=0.0004$) and mortality (1.62 [1.41 to 1.85]; $P<0.0001$) and lower independence (0.89 [0.80 to 0.99]; $P=0.04$) compared with Group 4. Group 3 had similar results as Group 1.

Conclusions—There is a strong association of high systolic BP after thrombolysis with poor outcome. Withholding antihypertensive therapy up to 7 days in patients with a history of hypertension was associated with worse outcome, whereas initiation of antihypertensive therapy in newly recognized moderate hypertension was associated with a favorable outcome. **(*Stroke*. 2009;40:2442-2449.)**

Key Words: antihypertensive ■ blood pressure ■ infarction ■ ischemia ■ stroke ■ thrombolysis

The optimal management of blood pressure (BP) during the acute phase of stroke is still not well established. The general message in guidelines is not to intervene unless for extreme BP values or unusual medical conditions.[1,2] This conservative attitude is based on observations that BP usually settles without intervention during the first week after hospitalization,[3,4] and on our limited understanding of the complex pathophysiology of elevated BP during acute stroke. In

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hypertensive patients, cerebral autoregulation is potentially shifted to a higher level,[5] whereas in the ischemic penumbra, cerebral autoregulation is disrupted and cerebral perfusion pressure is directly related to systemic BP.[6] There is fear of reducing cerebral perfusion pressure, which is critical for cerebral blood flow in the penumbral zone,[7] in particular in light of adverse effects of BP-lowering using nimodipine in the acute phase of stroke.[8–10]

There are several unanswered questions about the management of hypertension during the acute phase of stroke: Should ongoing antihypertensive therapy be continued? Should antihypertensive therapy be initiated in newly recognized high BP? If yes, what threshold level of BP would be required to justify antihypertensive treatment?[2] These issues have been discussed for decades, but unfortunately, recommendations are still weak due to lack of adequate evidence from randomized, controlled trials (RCTs) and variable outcome results from small observation studies[9,11] and a systematic review.[12]

These questions are also highly relevant for patients treated with intravenous thrombolysis because of the concern that increasing BP during and early after thrombolysis could increase the risk of hemorrhage.[13–15] Intravenous alteplase is the only approved pharmacological treatment for acute ischemic stroke. The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) shows that intravenous thrombolysis is safe and effective in routine clinical practice when used within 3 hours of symptom onset even by centers with little previous experience of stroke thrombolysis.[16] The recent SITS–International Stroke Thrombolysis Register (ISTR)[17] study and European Cooperative Acute Stroke Study III (ECASS III)[18] show benefit of thrombolysis up to 4.5 hours of symptom onset. More patients will be treated with thrombolysis in routine clinical practice and therefore evidence to guide BP management is urgently needed. According to the European Summary of Product Characteristics, thrombolysis is contraindicated in patients with ischemic stroke with systolic BP levels >185 mm Hg and/or diastolic BP >110 mm Hg, although intervention is permitted to control BP acutely to this level. Current European Stroke Organization[1] and American Stroke Association[2] guidelines recommend treatment intervention if systolic BP exceeds 180 mm Hg or diastolic BP exceeds 105 mm Hg during and early after thrombolysis treatment.

In the absence of data guiding BP management during and after intravenous thrombolysis in acute ischemic stroke, we decided to explore our extensive observational database retrospectively. The purpose of this analysis was to examine the relationship of BP and antihypertensive therapy with outcomes in patients with and without a history of hypertension treated with intravenous thrombolysis using the SITS-ISTR.[19]

Methods

Study Population

All patients registered in SITS-ISTR between December 2002 and October 2007 were included in the study. Details of the methodology, including data collection and management for SITS-ISTR and SITS-MOST, have been described previously.[16] In short, SITS-ISTR is a prospective, multinational Internet-based register for patients treated with thrombolysis after acute ischemic stroke.[19] Baseline and demographic characteristics, stroke severity measure by National Institutes of Health Stroke Scale (NIHSS) score (possible range 0 to 42, with 0 representing normal neurological function and 42 maximal deficit), time intervals, risk factors, medication history, and admission and follow-up imaging scans data were documented. BP was recorded at baseline, 2 hours, and 24 hour after thrombolysis. BP measurement followed standard clinical practice with no centrally provided instruction. Antihypertensive therapy was recorded at baseline and within 7days after thrombolysis. Outcome measurements included NIHSS at 2 hours, 24 hours, and 7 days; modified Rankin score at 3 months; and presence of hemorrhage on follow-up imaging scans.

Ethical Consideration and Source Data Verification

Because SITS-ISTR is an ongoing audit of stroke thrombolysis, approval from regulatory authorities and ethics committees, and patient informed consent, is not always mandatory. The requirements differ among participating countries. Approvals were obtained in countries where required. The SITS-MOST study was approved by the Ethics Committee of the Karolinska Institute in Stockholm, Sweden, as well as by the Swedish Medical Products Agency.

The SITS International Coordination Office performed regular online monitoring of the SITS-ISTR data. Moreover, monthly downloads of individual patient data were checked for error or inconsistency. A total of 6483 patients in the present study was from SITS-MOST in which sample source data verification was performed by monitors under the supervision of national coordinators.

Definitions and Classifications

In the present study, history of hypertension was defined by either history of hypertension (n=6670) or treatment with antihypertensives at stroke onset (n=5320, 90% of these patients had a history of hypertension). Of 5320 patients who received antihypertensives at baseline, 4683 patients received only oral, 345 patients only intravenous, and 292 both oral and intravenous therapies.

Within 7 days, 4715 patients received only oral antihypertensive therapy, 409 patients were treated with only intravenous antihypertensive therapy, and 1263 patients received both oral and intravenous antihypertensive therapy.

Patients were categorized according to the history of hypertension and antihypertensive therapy within 7 days after thrombolysis: Group 1, patients with a history of hypertension treated with antihypertensive therapy (n=5612); Group 2, patients with a history of hypertension not treated with antihypertensive therapy (n=1573); Group 3, patients without a history of hypertension treated with antihypertensive therapy (n=995); and Group 4, patients without a history of hypertension not treated with antihypertensive therapy (n=2632). Subdivision into these 4 groups was performed to enable us to study the effect of antihypertensive therapy in patients with and without a history of hypertension based on the ongoing discussion in the literature for decades.[2]

In 617 patients, information on antihypertensive therapy within 7 days after thrombolysis was missing and we used the principle of the last value carried forward from baseline. Of these, 328 (53.2%) received antihypertensive therapy at stroke onset, 283 (45.9%) did not, and in 6 (0.97%), treatment was not known.

Postthrombolysis systolic BP and diastolic BP were defined as the average of values at 2 hours and 24 hours.

Outcome Measurements

Outcome measurements were:

1. Symptomatic (NIHSS deterioration ≥4 points or death within 24 hours) intracerebral hemorrhage Type 2 in the 22- to 36-hour follow-up imaging scans after the start of thrombolysis treatment, termed the SITS-MOST definition.[16] This conservative definition was included in the SITS-MOST study

Table 1. Baseline Characteristics for All Patients and Categorized by History of Hypertension and Antihypertensive Therapy Within 7 Days After Thrombolysis

Data are Median (IQR) or n/N (%)	All Patients (n=11 080)	Group 1 (n=5612) Patients With a History of Hypertension Treated With Antihypertensives	Group 2 (n=1573) Patients With a History of Hypertension Not Treated With Antihypertensives	*P* Value Group 1 Versus Group 2	Group 3 (n=995) Patients Without a History of Hypertension Treated With Antihypertensives	Group 4 (n=2632) Patients Without a History of Hypertension Not Treated With Antihypertensives	*P* Value Group 3 Versus Group 4
Age, years	70 (60–76)	72 (64–77)	71 (62–77)	<0.001	68 (59–75)	62 (50–72)	<0.001
Gender, female	4594/11 080 (41.5)	2440/5612 (43.5)	675/1573 (42.9)	0.71	362/995 (36.4)	1024/2632 (38.9)	0.18
Blood glucose	117 (102–141)	121 (104–148)	118 (102–143)	<0.001	115 (101–137)	110 (97–128)	<0.001
NIHSS	13 (8–18)	12 (8–17)	15 (9–19)	<0.001	12 (8–17)	12 (8–17)	0.32
Diabetes mellitus	1893/10 896 (17.4)	1300/5525 (23.5)	304/1551 (19.6)	0.001	104/992 (10.5)	161/2623 (6.1)	<0.001
Hyperlipidemia	3352/9653 (34.7)	2105/4861 (43.3)	511/1396 (36.6)	<0.001	201/890 (22.6)	493/2370 (20.8)	0.29
Atrial fibrillation	2800/10 776 (26.0)	1743/5440 (32.0)	410/1538 (26.7)	<0.001	235/971 (24.2)	367/2591 (14.2)	<0.001
Previous stroke	1359/10 906 (12.5)	841/5510 (15.3)	219/1551 (14.2)	0.28	81/989 (8.2)	191/2609 (7.2)	0.42
Smoking	4210/10 325 (40.8)	1890/5166 (36.6)	588/1477 (39.8)	0.03	419/944 (44.4)	1196/2509 (47.7)	0.09
Aspirin	3387/10 963 (30.9)	2253/5546 (40.6)	499/1557 (32.1)	<0.001	193/988 (19.5)	405/2622 (15.5)	0.004
Congestive heart failure	880/10 814 (8.1)	607/5460 (11.1)	124/1540 (8.1)	0.001	60/982 (6.1)	81/2598 (3.1)	<0.001
Onset to treatment time	145 (115–170)	143 (115–168)	145 (120–170)	0.007	145 (115–165)	145 (119–170)	0.27
Systolic BP	151 (138–168)	160 (142–170)	150 (135–165)	<0.001	154 (140–168)	140 (130–157)	<0.001
Diastolic BP	82 (74–90)	84 (75–93)	80 (71–90)	<0.001	84 (77–90)	80 (71–90)	<0.001

IQR indicates interquartile range.

protocol and agreed with the European regulatory authority European Medicines Evaluation Agency. We consider that it best reflects bleeds that are genuinely likely to have been caused by thrombolysis and to have caused noticeable deterioration;

2. Symptomatic (any NIHSS deterioration or death within 7 days) hemorrhage of any type in any posttreatment imaging scans after start of thrombolysis treatment, termed the RCT definition.[13,20] This is an inclusive definition that ensures that no potential hemorrhagic complication is overlooked and is provided for comparison with published RCT data;
3. Death within 3 months (modified Rankin Score=6); and
4. Independence for activities of daily living (modified Rankin Score 0 to 2) at 3 months.

Statistical Testing

Descriptive statistics for baseline and demographic data were presented for all patients and according to history of hypertension and antihypertensive therapy within 7 days after thrombolysis. For categorical variables, proportions (%) were calculated by dividing the number of events with the total number excluding missing or unknown cases. For calculation of a statistically significance difference between proportions, we used the χ^2 method and for medians, we used the Mann–Whitney *U* test. Multivariable analyses were performed to examine the association between BP as continuous as well as categorical variables and dichotomized outcomes. For each outcome, a separate multivariable analysis was performed after adjustment for the following variables: age, gender, diabetes mellitus, hyperlipidemia, atrial fibrillation, congestive heart failure, previous stroke, independency before current stroke measured by modified Rankin Score 0 to 1, smoking, aspirin treatment at stroke onset, antiplatelet other than aspirin, baseline NIHSS, baseline blood glucose, body weight, categorized by history of hypertension and antihypertensive therapy within 7days after thrombolysis, signs of current infarction in the baseline imaging study, and stroke onset to treatment time.

In the univariate analysis, the upper and lower limits of the CIs used a score method with continuity correction[21] for calculation of the 95% CIs of proportions for symptomatic intracerebral hemorrhage (SICH), mortality, and independence. All analyses were performed using STATISTICA software, Version 8.0. Multivariable analyses were performed by logistic regression analysis using generalized linear or nonlinear models.

Results

Patients and Demographics

In total, 11 080 patients with ischemic stroke treated with intravenous thrombolysis with confirmed baseline data were recorded in SITS-ISTR at 403 centers from 28 countries, of whom 96.4% (10 686 of 11 080) were from Europe.

Table 1 shows the baseline characteristics for all patients and is categorized by history of hypertension and antihypertensive therapy within 7 days after thrombolysis.

BP as a Continuous Variable and Its Association With Main Outcomes

Figure 1 shows BP course by main outcome parameters. Systolic BP was consistently higher in patients with poor outcomes. The diastolic BP course was similar in patients with good and poor outcomes at 3 months.

There was no statistical significant difference in systolic BP course between patients with early (2 hours after thrombolysis) and late (after 2 hours) onset of symptomatic hemorrhage per SITS-MOST (baseline 160 versus 157 [$P=0.32$], 2 hours 160 versus 158 [$P=0.63$], and 24 hours 152 versus 155 [$P=0.67$]) or symptomatic hemorrhage per RCT definition (baseline 156 versus 154 [$P=0.31$], at 2 hours 154 versus 153 [$P=0.52$], and at 24 hours 152 versus 149 [$P=0.14$]).

In the multivariable analysis, average high systolic BP at 2 to 24 hours was associated with high rates of symptomatic hemorrhage per SITS-MOST definition ($P<0.0001$), symptomatic hemorrhage per RCT ($P<0.0001$), mortality at 3 months ($P=0.0004$), and low rates of functional independence ($P<0.0001$). In the multivariable analysis

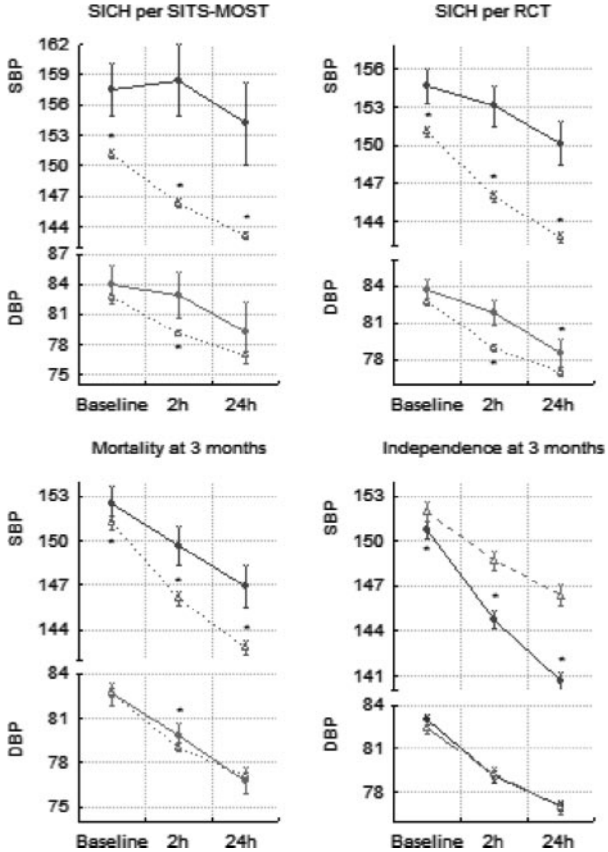

Figure 1. BP course by main outcome**.** Mean (midpoints) and 95% CIs (vertical error bars) of BP course by main outcomes. Opaque rounds with continued lines were events and transparent triangles with broken lines were nonevents. Events were SICH per SITS-MOST (NIHSS score deterioration ≥4 points within 24 hours plus intracerebral hemorrhage Type 2), SICH per RCT (any hemorrhage plus any neurological deterioration), mortality, and functional independence (modified Rankin Score 0 to 2) at 3 months. Asterisk (*) represents the statistically significant difference at the 5% level ($P<0.05$) between the events and nonevent.

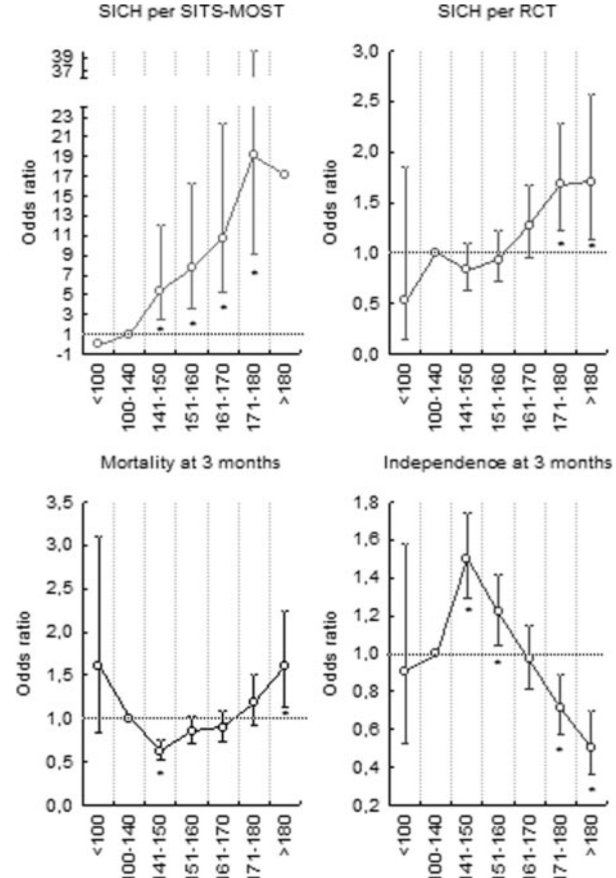

Figure 2. Adjusted OR (midpoints) and 95% CIs (vertical error bars) derived from multivariable analysis for main outcomes categorized by average postthrombolysis systolic BP (SBP) within 24 hours. SICH per SITS-MOST was defined by NIHSS score deterioration ≥4 points within 24 hours plus intracerebral hemorrhage Type 2, SICH per RCT was defined by any hemorrhage plus any neurological deterioration; mortality and functional independence was defined by modified Rankin Score 0 to 2 at 3 months. Asterisk (*) above or below the respective error bars represents the statistically significant difference at the 5% level ($P<0.05$) between the SBP category with the reference SBP (100 to 140 mm Hg).

when baseline BP was entered alone in the model, high baseline systolic BP was associated with high rates of symptomatic hemorrhage per SITS-MOST definition ($P=0.03$) and symptomatic hemorrhage per RCT ($P=0.02$) and high baseline diastolic BP with high rate of mortality at 3 months ($P=0.02$).

BP as a Categorized Variable and Its Association With Main Outcomes

Based on the strong association with outcome of postthrombolysis average systolic BP up to 24 hours, and the possibility of nonlinearity of the association between BP and outcome, patients were further categorized as follows: systolic BP <100 mm Hg (n=64), 100 to 120 mm Hg (n=1024), 121 to 140 mm Hg (n=3414), 141 to 150 mm Hg (n=2137), 151 to 160 mm Hg (n=1769), 161 to 170 mm Hg (n=1215), 171 to 180 mm Hg (n=656), and >180 mm Hg (n=243). Because systolic BP >140 mm Hg is generally accepted as hypertension, we categorized systolic BP >140 mm Hg by each 10 mm Hg. In the multivariable analysis, systolic BP 100 to 140 mm Hg was used as the reference group for calculation of ORs.

Figure 2 shows the adjusted ORs derived from multivariable analysis of main outcomes for the systolic BP categories. For symptomatic hemorrhage rates, the association between systolic BP increase and the OR was almost linear; the higher the systolic BP, the greater the risk of symptomatic hemorrhage. For mortality and functional independence at 3 months, the association between systolic BP increase and the OR was U-shaped and bell-shaped, respectively. The best outcome (lowest mortality and highest independency) was observed in patients with systolic BP values 141 to 150 mm Hg. The adjusted OR for symptomatic hemorrhage per SITS-MOST definition was 4 times higher for patients with a postthrombolysis systolic BP exceeding 170 mm Hg compared with those within the interval of 141 to 150 mm Hg. For symptomatic hemorrhage per RCT definition and for mortality at 3 months, the ORs were double and for the rate of independence at 3 months, the OR was less than half when systolic BP exceeded 170 mm Hg compared with those within the interval of 141 to 150 mm Hg.

Table 2. Univariate Outcome Results (Percentage and 95% CIs) for All Patients and Categorized by History of Hypertension and Antihypertensive Therapy Within 7 Days After Thrombolysis*

	All Patients	Group 1: Patients With a History of Hypertension Treated With Antihypertensives	Group 2: Patients With a History of Hypertension Not Treated With Antihypertensives	*P* Value Group 1 Versus Group 2	Group 3: Patients Without a History of Hypertension Treated With Antihypertensives	Group 4: Patients Without a History of Hypertension Not Treated With Antihypertensives	*P* Value Group 3 Versus Group 4
SICH per SITS-MOST†	181/10 928	109/5538	41/1540	0.09	7/989	21/2605	0.76
	1.66% (1.43–1.92)	1.97 (1.63–2.38)	2.66 (1.94–3.63)		0.71 (0.31–1.52)	0.81 (0.52–1.26)	
SICH per RCT‡	825/10 902	477/5527	148/1531	0.21	52/989	133/2599	0.86
	7.57% (7.08–8.09)	8.6 (7.9–9.4)	9.7 (8.3–11.3)		5.3 (4.0–6.9)	5.1 (4.3–6.1)	
Mortality at 3 months	1420/9664	724/4876	315/1374	<0.0001	72/885	262/2299	0.007
	14.7% (14.0–15.4)	14.9 (13.9–15.9)	22.9 (20.8–25.3)		8.1 (6.5–10.2)	11.4 (10.1–12.8)	
Independence (modified Rankin Score 0–2) at 3 months	4902/9533 51.4% (50.4–52.4)	2365/4816 49.1 (47.7–50.5)	588/1357 43.3 (40.7–46.0)	0.0002	501/870 57.6 (54.2–60.9)	1352/2266 59.7 (57.6–61.7)	0.29

**P* values were calculated by comparing Group 1 with Group 2 and Group 3 with Group 4.

†Per SITS-MOST definition, a deterioration of NIHSS score of ≥4 and Type 2 intracerebral hemorrhage on 22–36 hours posttreatment imaging scans.

‡Per RCT, any NIHSS worsening within 7 days and any hemorrhage.

Postthrombolysis Antihypertensive Therapy Within 7 Days and Its Association With Outcome in Patients With and Without a History of Hypertension

In total, 10 812 patients could be classified by history of hypertension and antihypertensive therapy after thrombolysis, whereas 268 (2.4%) patients could not be classified due to unknown or missing data. Table 1 shows that patients with a history of hypertension (Groups 1 and 2) compared with patients without such a history (Groups 3 and 4) were older, had higher levels of blood glucose, higher prevalence of diabetes mellitus, hyperlipidemia, atrial fibrillation, congestive heart failure, previous stroke, and use of aspirin before the current stroke.

Table 2 shows the univariate results of the main outcomes for all patients and hypertension groups. Patients without a history of hypertension treated with antihypertensive therapy within 7 days after thrombolysis (Group 3) had similar outcomes as patients without a history of hypertension who were not treated with antihypertensive therapy (Group 4). The worst outcome was seen in patients who had a history of hypertension but did not receive antihypertensive therapy after thrombolysis (Group 2).

Figure 3 shows adjusted ORs derived from multivariable analysis of outcomes for hypertension groups. Patients with a history of hypertension not treated with antihypertensive therapy (Group 2) had the worst outcome. Patients without a history of hypertension treated with antihypertensive therapy (Group 3) had lower mortality, a trend to a higher functional independence rate, and lower rates of symptomatic hemorrhage.

In a sensitivity analysis, we considered only patients enrolled in SITS-MOST but found no appreciable difference in the trends observed.

Discussion

Our results, based on the largest database on intravenous thrombolysis for acute ischemic stroke, emphasize the strong association of postthrombolysis systolic BP as a continuous variable during the first 24 hours after thrombolysis not only with the incidence of symptomatic hemorrhage, but also with mortality and functional independence at 3 months follow-up. Postthrombolysis high systolic BP up to 24 hours as a continuous variable was associated with poor outcome in all parameters. When systolic BP was categorized, the higher the systolic BP, the higher the risk of symptomatic hemorrhage. For mortality and independence, the relationship was U-shaped with systolic BP 141 to 150 mm Hg associated with the most favorable results, and although the rate of symptom-

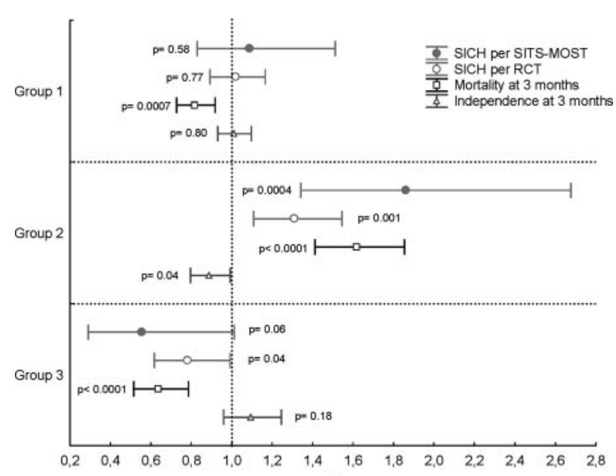

Figure 3. Main outcomes categorized by history of hypertension and antihypertensive therapy. Group 1, patients with a history of hypertension treated with antihypertensives; Group 2, patients with a history of hypertension withholding antihypertensives; Group 3, patients without a history of hypertension treated with antihypertensives; and Group 4, patients without a history of hypertension not treated with antihypertensive (reference group). Adjusted OR, the midpoints, and their 95% CIs (horizontal errors bars) derived from multivariable analysis of outcome. SICH per SITS-MOST: NIHSS score deterioration ≥4 points within 24 hours plus intracerebral hemorrhage Type 2, SICH per RCT: any hemorrhage plus any neurological deterioration. Mortality and functional independence (modified Rankin Score 0 to 2) at 3 months. For SICH and mortality, OR <1.0 means outcome was better (lower SICH and mortality) than Group 4. For independence, OR <1.0 means outcome was worse (lower independence) than Group 4.

atic hemorrhage declined at even lower systolic BP levels, this interval appeared in our observational study as the optimal level of BP postthrombolysis. Previous studies of patients with stroke not receiving thrombolysis observed most favorable outcomes were associated with a baseline systolic BP approximately 150 mm Hg.[22,23]

We also found that providing antihypertensive therapy after intravenous thrombolysis in patients with either a history of hypertension (Group 1) or moderately elevated BP without a history of hypertension (Group 3) did not seem to affect outcomes adversely; in contrast, withholding antihypertensive therapy in patients with a history of hypertension (Group 2) was associated with high mortality, a high symptomatic hemorrhage rate, and a low rate of functional independence. This finding was confirmed in the multivariable analysis after adjustment for other prognostic factors. In contrast, Brott et al[15] (n=624) found that postrandomization antihypertensive therapy for thrombolysis-treated patients was associated with less favorable outcomes compared with those who were hypertensive and did not receive antihypertensive therapy. Lindsberg et al[24] (n=75) also found that using antihypertensive therapy after thrombolysis reduced the likelihood of favorable outcome. These studies were smaller than ours and applied different outcome measures.

The BP course differed between patients with good and bad outcomes. The differences were more pronounced for systolic BP than for diastolic BP suggesting that moderate systolic BP change influences outcome parameters more than moderate diastolic BP change in stroke thrombolysis. In previous studies, diastolic BP reduction was associated with poor outcome.[9,10,24] In our present study, those who had symptomatic hemorrhage had a significantly higher baseline systolic BP compared with patients without symptomatic hemorrhage. The systolic BP did not decline significantly up to 24 hours from baseline in patients classified as symptomatic hemorrhage per SITS-MOST definition and at 2 hours in patients classified as symptomatic hemorrhage per RCT definition. Systolic BP course was similar whether or not paralleled by an early neurological deterioration, suggesting that the postthrombolysis high systolic BP cannot primarily be explained as secondary to the hemorrhage and that the high systolic BP may instead contribute to the cause of symptomatic hemorrhage. This conclusion is also supported by our previous finding that baseline systolic BP is an independent prognostic factor for symptomatic hemorrhage.[25] For mortality and independence, systolic BP at baseline was slightly higher in patients with poor outcome compared with patients with better outcome, but the difference between the groups was more obvious at 2 hours and 24 hours, indicating that systolic BP reduction after thrombolysis had an association with better outcome. Our results are consistent with intravenous thrombolysis studies in which lower 72-hour systolic BP was associated with favorable outcome.[26,27] In a study of intra-arterial thrombolysis, systolic BP 12 hours after intraarterial thrombolysis was lower in patients with vessel recanalization compared with persistent occlusion and the authors concluded that systolic BP remains higher when recanalization fails.[28] Vessel recanalization is an important predictor for outcome,[29] but complete vessel recanalization occurs in approximately 27% of patients treated with intravenous thrombolysis.[30,31] Therefore, our results cannot be explained simply by vessel recanalization.

The associations of pre- and postthrombolysis BP with outcomes are complex. The SITS-MOST multivariable study reported that high baseline systolic BP was associated with high rates of symptomatic hemorrhage but not with 3-month outcome.[25] A similar observation was made in the present study when postthrombolysis BP was not included in the multivariable model. Because pre- and postthrombolysis BP are highly correlated, the importance of prethrombolysis BP cannot be overruled. However, these unselected data suggest closer control of postthrombolysis systolic BP. Our findings are consistent with an intravenous thrombolysis study[31] and a rather large study in general stroke patients (n=1455)[32] but not with smaller studies (n <400).[33,34]

In our study, BP was measured according to usual clinical practice. This is likely to be less accurate than rigorously controlled methods and will therefore underestimate any true difference between groups or change over time. We found that patients with stroke with a history of hypertension had high prevalence of poor prognostic factors at baseline compared with patients without such a history. We subdivided patients to study the effect of antihypertensive treatment in patients with and without a history of hypertension. As expected, the prognostic factors in the 4 groups differed. However, between the 2 groups without a history of hypertension (Groups 3 and 4), baseline prognostic factors disadvantaged the newly treated antihypertensive group (Group 3) because the latter had equal stroke severity but were 6 years older, had higher blood glucose, and included more patients with diabetes, atrial fibrillation, or heart failure compared with Group 4 (no antihypertensive therapy). Despite this, outcomes in the treated group (Group 3) were as good as or better than those of untreated patients (Group 4). Likewise, despite similar risk profiles between antihypertensive treated and untreated patients with a history of hypertension (Group 1: with antihypertensive therapy and Group 2: withholding antihypertensives therapy)—because stroke severity favored the treated group but age diabetes, atrial fibrillation, and heart failure favored the untreated patients—outcomes in the treated hypertensives were better than in the untreated group.

We believe these results shed light on some of the unanswered questions about the management of BP during the acute phase of stroke in patients treated with intravenous thrombolysis. However, there are limitations to our study. First, this is an observational explorative study based on retrospective analysis. Like with any register, reporting bias cannot be totally excluded, although specific measures were taken to reduce it. Reporting of all subsequent cases was a formal undertaking for participation in SITS, and its importance was emphasized during educational events. Regular online monitoring was performed as well as analysis of monthly downloads of the database. A total of 6483 patients (61%) was from SITS-MOST in which sample source data verification was performed by monitors. Our sensitivity analysis offers reassurance that sampling bias is unlikely to account for our findings. Second, because this is not a RCT, we found, as expected, that the groups with and without a history of hypertension and antihypertensive treatment were imbalanced at baseline. We performed multivariable analysis to adjust for these imbalances when evaluating outcome. However, it should be noted that multivariable analysis may not account for all imbalances. Third, we did not know the exact time when patients were treated with antihypertensive therapy within 7 days after thrombolysis. Therefore, we cannot propose the optimal time to initiate antihypertensive therapy after stroke thrombolysis. Fourth, we did not record the type of antihypertensive drug used for intervention and antihypertensive drugs given for other indication such as congestive heart failure and angina pectoris. Finally, missing data may also have influenced the results. Despite these limitations, it is worth noting that our study was based on the largest database for stroke thrombolysis so far and data were collected prospectively. Some of the ongoing trials[35,36] may answer some of these uncertainties.

Conclusion

Our results suggest a more active BP-lowering approach early after intravenous thrombolysis than reflected by current guidelines. However, due to potential limitations of observational studies, results from RCTs are required for a definitive recommendation.

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