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Blood Pressure and Clinical Outcomes in the International Stroke Trial

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Background and Purpose—Among patients with acute stroke, high blood pressure is often associated with poor outcome, although the reason is unclear. We analyzed data from the International Stroke Trial (IST) to explore the relationship between systolic blood pressure (SBP), subsequent clinical events over the next 2 weeks, and functional outcome at 6 months in patients with acute stroke.

Methods—We included in the analysis 17 398 patients from IST with confirmed ischemic stroke. A single measurement of SBP was made immediately before randomization. Clinical events within 14 days of randomization were recorded: recurrent ischemic stroke, symptomatic intracranial hemorrhage, death resulting from presumed cerebral edema, fatal coronary heart disease, and death. Survival and dependency were assessed at 6 months. Outcomes were adjusted for age, sex, clinical stroke syndrome, time to randomization, consciousness level, atrial fibrillation, and treatment allocation (aspirin, unfractionated heparin, both, or neither).

Results—A U-shaped relationship was found between baseline SBP and both early death and late death or dependency: early death increased by 17.9% for every 10 mm Hg below 150 mm Hg ($P<0.0001$) and by 3.8% for every 10 mm Hg above 150 mm Hg ($P=0.016$). The rate of recurrent ischemic stroke within 14 days increased by 4.2% for every 10-mm Hg increase in SBP ($P=0.023$); this association was present in both fatal and nonfatal recurrence. Death resulting from presumed cerebral edema was independently associated with high SBP ($P=0.004$). No relationship between symptomatic intracranial hemorrhage and SBP was seen. Low SBP was associated with a severe clinical stroke (total anterior circulation syndrome) and an excess of deaths from coronary heart disease ($P=0.002$).

Conclusions—Both high blood pressure and low blood pressure were independent prognostic factors for poor outcome, relationships that appear to be mediated in part by increased rates of early recurrence and death resulting from presumed cerebral edema in patients with high blood pressure and increased coronary heart disease events in those with low blood pressure. The occurrence of symptomatic intracranial hemorrhage within 14 days was independent of SBP. (*Stroke*. 2002;33:1315-1320.)

Key Words: blood pressure ■ brain edema ■ hemorrhage ■ recurrence ■ stroke, ischemic

In stroke-free individuals, the relationship between blood pressure and the occurrence of a first stroke¹ and the effect of blood pressure-lowering treatment in preventing first stroke² are well established. Higher blood pressure levels after stroke increase the risk of recurrent stroke,³ and recent trials indicate that treatment with blood pressure-lowering agents, specifically diuretics and/or angiotensin-converting enzyme inhibitors, is beneficial in reducing recurrence.⁴⁻⁶ In contrast, there is no reliable evidence from randomized, controlled trials to guide the management of blood pressure during the acute phase of stroke. Three quarters of patients with acute ischemic stroke have elevated blood pressure at presentation, of which about half have a history of hypertension.⁷ Blood pressure declines spontaneously over the first

week after stroke onset and returns to prestroke levels in two thirds of patients. Most studies, although not all, have found that high blood pressure, whether measured as casual or 24-hour ambulatory readings, in the acute phase of stroke is associated with a poor outcome.⁸⁻¹⁰ An explanation for these findings has not been given, although speculatively high blood pressure might promote early recurrence, hemorrhagic transformation, or the formation of cerebral edema.¹¹

The purpose of this study, a further analysis of data from the International Stroke Trial (IST),¹² was to characterize blood pressure in acute stroke, determine its relationship with outcome, and consider possible explanations. For clarity and to facilitate comparisons with other clinical series and cohorts, we restricted the analyses to patients with confirmed

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ischemic stroke, ie, those who had a CT scan performed before randomization that excluded primary intracranial hemorrhage.

Methods

International Stroke Trial

IST was a large randomized, single-blind, controlled, 3×2 factorial design trial assessing the safety and efficacy of aspirin, subcutaneous heparin (in 1 of 2 doses), or their combination compared with control.¹² In IST, 19 435 patients with acute presumed ischemic stroke were randomized within 48 hours of stroke onset from 467 hospitals in 36 countries. The primary outcomes were death by the end of treatment (within 14 days) and death or dependency at 6 months. We included 17 398 patients with CT-confirmed ischemic stroke in the following analyses. A single baseline measurement of systolic blood pressure (SBP) was recorded immediately before randomization in all subjects for use in the computer-based treatment allocation (minimization) algorithm.

Definitions

Definitions of outcomes are as given in the main IST publication¹²: (1) death resulting from any cause within 14 days; (2) death or dependency, ie, needing help from another person with daily activities, at 6 months;¹³ (3) ischemic stroke within 14 days, including any recurrent stroke of ischemic or unknown type; and (4) symptomatic intracranial hemorrhage (hemorrhagic stroke) within 14 days, including any recurrent stroke definitely caused by hemorrhage or symptomatic hemorrhagic transformation of the original infarct, that was confirmed by CT, MRI, or necropsy. We wanted to identify patients who deteriorated and died as a result of cerebral edema, although this was not coded as a specific cause of death in IST. For the purposes of this study, we attributed death to presumed cerebral edema if it occurred within 3 days of randomization from the index stroke, if it was not attributed to another cause (eg, recurrent stroke), and if the presenting stroke was nonlacunar. This definition was made before analysis. Local investigators recorded the occurrence of clinical events, including stroke and coronary heart disease events, up to and including 14 days in a nonblinded fashion.¹² Follow-up at 6 months was performed centrally and was effectively blinded to treatment allocation.¹²

Statistical Analysis

Data are given as mean (SD), median (semi-interquartile range), or frequency (percent). Statistical comparisons for continuous data were made by use of the independent-sample *t* test. For binary outcomes, the χ^2 test or, in cases of small expected frequencies, Fisher's exact test was used. Multivariate linear regression models were constructed to explore the relationship between baseline SBP and risk factors. Logistic regression models were constructed when the outcomes of interest were binary. Regression models were adjusted for known prognostic factors: age, sex, clinical syndrome [total anterior circulation syndrome (TACS)], time to randomization, level of consciousness, atrial fibrillation, and treatment group. Odds ratio [OR; 95% confidence intervals (CI), using a fixed model] refers to a 10-mm Hg increase in SBP. Analyses were performed with SPSS (SPSS Inc, version 9.0 for Windows).

Results

The trial recruited 19 435 patients with acute presumed ischemic stroke. For the purposes of the present analyses, we excluded 2037 patients for whom the final diagnosis was nonstroke, hemorrhagic stroke, or stroke of unknown type (ie, no CT scan or postmortem was performed).

The demographic and clinical details for the 17 398 included patients were reasonably representative of patients presenting to stroke services around the world (Table 1). The mean SBP at enrollment was 160.1 mm Hg (SD,

TABLE 1. Demographics, Clinical Characteristics, and Outcomes of 17 398 Patients With Confirmed Acute Ischemic Stroke

Characteristic	n (%)
Age, y	
<60	2769 (15.9)
60–69	4107 (23.6)
70–79	6091 (35.0)
80–89	4431 (25.5)
Sex	
Female	8015 (46.1)
Male	9383 (53.9)
SBP, mm Hg	
<120	735 (4.2)
120–139	2476 (14.2)
140–159	4859 (27.9)
160–179	4541 (26.1)
180–199	2933 (16.9)
>200	1854 (10.7)
Stroke syndrome	
Lacunar syndrome	4218 (24.3)
Partial anterior circulation syndrome	6985 (40.3)
TACS	4149 (23.9)
Posterior circulation syndrome	1996 (11.5)
Consciousness level	
Unconscious	246 (1.4)
Drowsy	3765 (21.6)
Alert	13 387 (77.0)
Stroke onset when	
Awake	12 246 (70.4)
Asleep	5152 (29.6)
Atrial fibrillation	
No	13 813 (82.8)
Yes	2865 (17.2)
Delay (from symptom onset to randomization), h	
<12	5377 (30.9)
12–23	4508 (25.9)
24–35	4758 (27.4)
36–48	2755 (15.8)
Outcome by 14 d	
Death from any cause	1484 (8.5)
Recurrent ischemic stroke (fatal or nonfatal)	382 (2.2)
Symptomatic intracranial hemorrhage (fatal or nonfatal)	48 (0.3)
Death from presumed cerebral edema	347 (2.0)
Outcome at 6 mo	
Death or dependency	10 707 (61.5)
Death from any cause	3736 (21.5)

27.5 mm Hg); thus, if the World Health Organization definition of hypertension (SBP >140 mm Hg) was used, 81.6% of patients had high blood pressure. The median time to randomization was 20 hours (semi-interquartile range, 10.5 hours). In univariate analyses, high blood pressure was

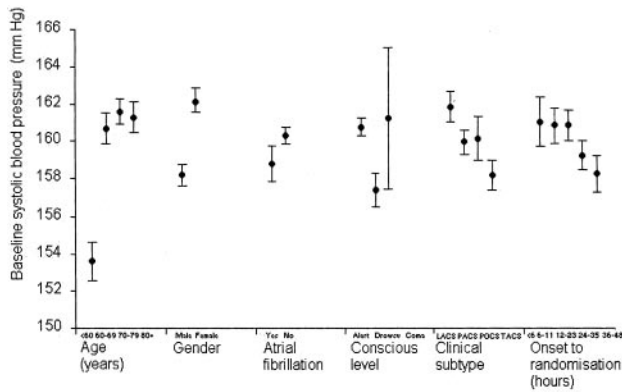


Figure 1. Mean baseline SBP (mm Hg) by age, sex, clinical syndrome, consciousness level, atrial fibrillation, and time to enrollment for 17 398 patients with confirmed acute ischemic stroke. Delay refers to the number of hours between stroke onset and randomization. Clinical syndrome of stroke categories refer to lacunar syndrome (LACS), partial anterior circulation syndrome (PACS), posterior circulation syndrome (POCS), and TACS. Squares indicate mean within each subgroup; 95% CIs are represented by T bars.

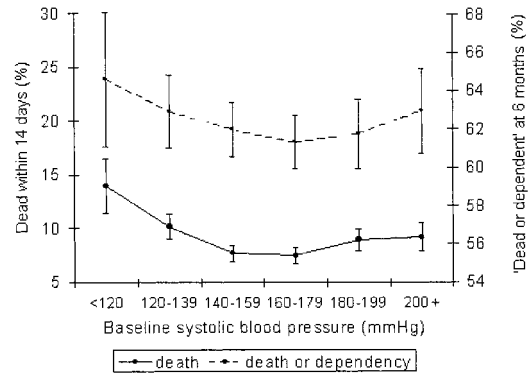


Figure 2. Proportion of patients who died within 14 days (solid lines) or were dead or dependent at 6 months (dashed lines) by baseline SBP. Circles and squares indicate the mean percentage of patients who had died within 14 days and patients who had died or were dependent at 6 months, respectively, within each blood pressure subgroup; 95% CIs are represented by T bars.

associated with several factors: female sex, early presentation, lacunar syndrome, alertness, and sinus rhythm (Figure 1). Conversely, TACS was associated with low blood pressure. By 14 days, 8.5% of patients had died, and by 6 months, 61.5% were dead or dependent (Table 1). The most frequent causes of death were the initial stroke, recurrent ischemic stroke, and pneumonia.

In univariate analyses, poor outcome (death within 14 days or death or dependency at 6 months) was associated with increasing age, most severe clinical syndrome (TACS), early presentation, and atrial fibrillation. In a multivariate model, age, TACS, early presentation, atrial fibrillation, and alertness were independent predictors of prognosis.

Blood Pressure and Outcome

A U-shaped relationship was found between baseline SBP and both primary outcomes of death within 14 days and death or dependency at 6 months (Figure 2). The lowest frequency of poor outcome occurred in patients with a baseline SBP of 140 to 179 mm Hg, with the nadir around 150 mm Hg, a value that we subsequently used as a reference point.

Patients with an SBP <150 mm Hg had, for every 10-mm Hg fall in blood pressure, an increased risk of early death of 17.9% ($P<0.0001$) and an increased risk of death or dependency at 6 months of 3.6% ($P=0.044$; Table 2). Above 150 mm Hg, the risk of early death increased by 3.8% for every 10-mm Hg increase in SBP ($P=0.016$), and there was a nonsignificant increase of 1.1% in 6-month death or dependency ($P=0.21$). The same pattern was found after adjustment for baseline prognostic factors, including age, sex, most severe clinical syndrome (TACS), time to randomization, level of consciousness, atrial fibrillation, and treatment (aspirin, heparin) (Table 2).

Blood Pressure and Intermediate Events

Recurrent ischemic stroke within 14 days was independently associated with increasing blood pressure (Figure 3); for every 10-mm Hg increase in SBP, the frequency of early recurrence increased by 4.2% ($P=0.023$; Table 3). Similar trends were seen for fatal ($P=0.10$) and nonfatal ($P=0.09$) recurrent ischemic stroke separately; hence, death within 14 days was not the governing factor for this relationship. In contrast, neither symptomatic intracranial hemorrhage ($P=0.14$) nor total recurrent stroke (recurrent ischemic stroke, symptomatic intracranial hemorrhage, or recurrent

TABLE 2. Relationship Between Early Death and Late Death or Dependency With SBP

Outcome	Blood Pressure, mm Hg	OR (95% CI)	
		Unadjusted	Adjusted
Death within 14 d	≤150	1.179 (1.124–1.235)	1.155 (1.095–1.216)
	≥150	1.038 (1.007–1.068)	1.048 (1.012–1.079)
Death or dependency at 6 mo	≤150	1.036 (1.000–1.072)	1.053 (1.012–1.095)
	≥150	1.011 (0.994–1.029)	1.009 (0.989–1.030)

ORs are expressed in terms of a 10-mm Hg difference relative to a reference value of 150 mm Hg. The relationship between blood pressure and outcome was adjusted for known prognostic factors: age, sex, most severe clinical syndrome (TACS), time to randomization, level of consciousness, atrial fibrillation, and treatment (aspirin, heparin). ORs greater than unity indicate a greater odds of death or death or dependency than patients with a baseline SBP of 150 mm Hg.

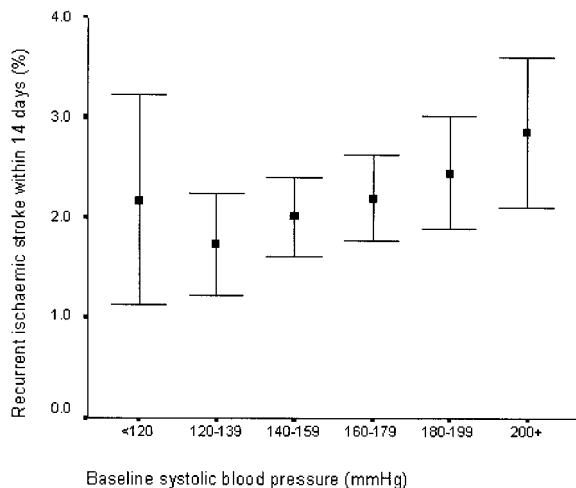


Figure 3. Frequency of recurrent ischemic stroke by SBP from 17 398 patients with confirmed acute ischemic stroke. Squares indicate mean within each SBP group; 95% CIs are represented by T bars.

stroke of unknown type; $P=0.63$) was associated with baseline SBP. In a multivariate model, death resulting from presumed cerebral edema was independently associated with SBP ($P=0.004$). We found no evidence of an interaction between treatment with aspirin, heparin, or both and blood pressure for the outcomes of recurrent ischemic stroke, death resulting from presumed cerebral edema, symptomatic intracranial hemorrhage, or fatal coronary heart disease.

The frequency of recurrent ischemic stroke within 14 days was not associated with clinical stroke syndrome; the rates were as follows: lacunar syndrome, 1.9% (95% CI, 1.5 to 2.3); TACS, 2.2% (95% CI, 1.7 to 2.6); partial anterior circulation syndrome, 2.2% (95% CI, 1.9 to 2.6); and posterior circulation syndrome, 2.8 (95% CI, 2.0 to 3.5). Most recurrent ischemic strokes occurred within 5 days of enrollment, with the peak rate on day 1 (data not shown). Early recurrent ischemic stroke was found to be strongly related to early death ($\chi^2=75.51$, $P<0.001$) and 6-month death or dependency ($\chi^2=45.71$, $P<0.001$).

Deaths resulting from coronary heart disease within 14 days were independently associated with low SBP ($P=0.002$; Table 3). This relationship was maintained after adjustment

for age, sex, clinical syndrome (TACS), atrial fibrillation, consciousness level, time to randomization, and treatment received.

Discussion

This work, involving a large cohort of $\approx 18\,000$ patients, both confirms and extends previous studies of blood pressure in acute ischemic stroke. First, it confirms that high blood pressure, measured at a median time of 20 hours after ictus, is common ($\approx 80\%$) in patients with acute ischemic stroke. Second, it supports previous findings that high blood pressure early after stroke is associated with poor outcome after stroke.⁸⁻¹⁰ A novel finding is that relatively low blood pressure (SBP <120 mm Hg), albeit an uncommon clinical finding ($\approx 5\%$ of patients), is also associated with poor outcome. Both relationships appear to be independent of prognostic factors such as age, stroke severity, level of consciousness, and atrial fibrillation.

We investigated possible explanations for the link between blood pressure and outcome. Higher blood pressures were associated with a significantly increased risk of recurrent ischemic stroke within 14 days; a patient with an enrollment SBP >200 mm Hg had a $>50\%$ greater risk of recurrence than one with a pressure of 130 mm Hg. Importantly, early recurrence was associated with poor subsequent outcome, thereby linking blood pressure at presentation with increased death or dependency at 6 months. Surprisingly, we did not find that the risk of subsequent symptomatic intracranial hemorrhage was related to early blood pressure levels as originally hypothesized.¹¹ Although the stroke complication of cerebral edema was not systematically recorded in IST, we developed a surrogate for this, ie, deaths occurring up to 3 days after enrollment (within 5 days of stroke onset) in patients with nonlacunar infarction. With this definition, death resulting from presumed cerebral edema was associated with higher blood pressures. On average, a 5.8% increase in the risk of death resulting from presumed cerebral edema was seen for every 10-mm Hg increase in blood pressure. Even though this definition of cerebral edema was retrospectively applied and indirect, its relationship with SBP was independent and robust.

We also sought explanations for the relationship between low blood pressure and outcome, although detailed analysis

TABLE 3. Relationship Between Recurrent Ischemic Stroke, Symptomatic Intracranial Hemorrhage, Death From Presumed Cerebral Edema, and Fatal Coronary Heart Disease With SBP

Events	OR (95% CI)	
	Unadjusted	Adjusted
Recurrent ischemic stroke	1.042 (1.007-1.078)	1.043 (1.006-1.081)
Symptomatic intracranial hemorrhage	0.995 (0.988-1.001)	0.998 (0.991-1.047)
Death from presumed cerebral edema	1.031 (0.993-1.070)	1.058 (1.019-1.097)
Death from coronary heart disease	0.989 (0.982-0.996)	0.990 (0.983-0.997)

ORs are expressed in terms of a 10-mm Hg difference. The relationship between blood pressure and outcome was adjusted for known prognostic factors: age, sex, clinical syndrome (total anterior circulation infarct), time to randomization, level of consciousness, atrial fibrillation, and treatment (aspirin, heparin). ORs greater than unity indicate that patients with a higher SBP have a higher odds of death than patients with a lower SBP.

was limited because of the small number of subjects with SBP <120 mm Hg. However, low blood pressure was associated with an excess of early deaths from coronary heart events. Low blood pressure may also have been associated with early cerebral reinfarction because there was a hint, albeit not statistically significant, that the relationship between blood pressure and recurrence is J-shaped rather than linear (see Figure 3). We also observed a higher proportion of TACS among patients with low blood pressure, a stroke presentation known to have a poor prognosis.¹² It is unclear whether these are causal associations. For example, low blood pressure could promote reduced cerebral and cardiac perfusion, leading to their infarction and a poor outcome. Alternatively, myocardial ischemia can cause hypotension and therefore cerebral hypoperfusion, larger infarcts, and poor outcome.

This study has a number of methodological weaknesses that might have modulated some of the findings. First, IST was a randomized, controlled trial; therefore, patients were selected as opposed to belonging to an unselected consecutive cohort. However, the inclusion criteria were broad and did not specify blood pressure limits. Because antithrombotic drugs (aspirin and/or unfractionated heparin) were involved, patients with a definite need for (eg, acute coronary syndrome, pulmonary embolism) or contraindication to these drugs would have been excluded; investigators may also have excluded patients with severely elevated blood pressure because of a perception that they might be at increased risk of bleeding. They may also have excluded patients with severe comorbid disease, eg, heart failure. As a result, patients with low or high blood pressure may have been underrepresented in IST, thereby potentially weakening rather than exaggerating the relationship between blood pressure and outcome. We used both univariate and multivariate models to describe the relationships between blood pressure and outcome; the multivariate analyses included 6 prognostic clinical variables (age, sex, clinical syndrome, time to randomization, level of consciousness, and atrial fibrillation) that should have tended to correct for the effects of patient selection. Second, diastolic blood pressure was not recorded in IST, so we could not determine the relationship between it (or derivatives of it, eg, mean arterial blood pressure, pulse pressure, and pulsatility index, and SBP) and outcome. Third, a single measure only of SBP was made for each patient, so we could not adjust the findings for regression dilution bias. Allowing for regression to the mean, it is likely that the relationships between blood pressure and subsequent events would have been stronger, as found for essential hypertension and first stroke.¹ Although the measurement of blood pressure was made in a nonstandardized manner and at a variable time within the first 48 hours of stroke onset, this approach would have introduced a greater random error rather than a systematic bias. Fourth, IST was unblinded, and events occurring within 14 days, including stroke recurrence and symptomatic hemorrhage, and coronary heart disease events were ascertained by local investigators. Hence, it is possible that interpretation and recording of these events were biased by knowledge of treatment assignment or by baseline blood pressure readings. However, because such bias would be more evident for nonfatal events and because

the observed relationship between blood pressure and recurrent ischemic stroke were similar for fatal and nonfatal effects, the size of any such recording bias is likely to have been small. Last, we had to create a priori a definition for identifying patients who are likely to have had cerebral edema, a postulated mechanism by which high blood pressure in acute stroke might be detrimental,¹¹ because this end point was not measured in IST. This definition is inevitably weak but has merit because it focuses on patients with probable severe cerebral edema, ie, those who die early after stroke.

On the other hand, the data set has a number of strengths. The data were prospectively collected and are virtually complete with negligible loss to follow-up, and the sample size was large. Furthermore, the sample was drawn from many different countries; therefore, the findings are potentially of wider relevance than observations from a single center or country.

Whether altering blood pressure can improve outcome was not assessed in this observational study. Patients with low blood pressure might benefit from having it raised, perhaps with fluids (taking care not to exacerbate any heart failure), with an inotrope (providing clinical cardiac ischemia is not present), or by the cessation of prior antihypertensive medication. Conversely, those with higher pressures might have a better outcome if they continued prior antihypertensive medication or if their blood pressure was actively lowered with an appropriate drug. The use of calcium channel blockers in acute ischemic stroke was associated with a worsening of outcome in some studies,^{14–16} perhaps because they can reduce cerebral perfusion.¹⁷ Nevertheless, other classes of hypotensive drugs have shown promise in pilot studies,^{18–20} and lowering blood pressure was apparently not detrimental in the NINDS trial of alteplase.²¹ Such uncertainties mean that further randomized evidence is required, and a large trial of lowering blood pressure (excluding patients with lower levels of pressure) and stopping or continuing prior antihypertensive medication is currently underway.²² The effect of raising blood pressure with dobutamine is being assessed in a pilot trial.²³

In summary, both high blood pressure and low blood pressure were associated with poor outcome after acute ischemic stroke in this cohort. The risks of early recurrent stroke and death resulting from presumed cerebral edema but not symptomatic intracranial hemorrhage were increased with high blood pressure. Low blood pressure was associated with early fatal coronary heart disease events.

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