Effects of Blood Pressure and Blood Pressure–Lowering Treatment During the First 24 Hours Among Patients in the Third International Stroke Trial of Thrombolytic Treatment for Acute Ischemic Stroke

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**Background and Purpose**—In patients with acute ischemic stroke, a high blood pressure or a highly variable blood pressure is a common reason for withholding thrombolytic treatment, but guidelines recommend a conservative approach to active blood pressure lowering in this setting. We have performed exploratory analyses to study the clinical effects of blood pressure and early blood pressure–lowering treatment in patients included in a randomized-controlled trial of thrombolytic treatment for acute ischemic stroke.

**Methods**—The Third International Stroke Trial (IST-3) randomized 3035 patients with ischemic stroke to recombinant tissue-type plasminogen activator 0.9 mg/kg or open control within 6 hours of symptom onset. Blood pressure was measured at randomization, at start of treatment, and at 30 minutes and 1 and 24 hours after start of treatment, and the use of blood pressure–lowering treatment during the first 24 hours was recorded. We have characterized blood pressure by mean systolic blood pressure at baseline, by variability of systolic blood pressure (expressed by the standard deviation and the range between the lowest and the highest pressure), and by the change in systolic blood pressure from baseline to 24 hours. We used logistic regression analysis to explore the associations of blood pressure characteristics or blood pressure–lowering treatment with early adverse events, early death, and functional outcome at 6 months, after adjustment for key prognostic variables.

**Results**—High baseline blood pressure and high blood pressure variability during the first 24 hours were associated with higher numbers of early adverse events and early deaths, and for several analyses, the differences were statistically significant. A larger decline in blood pressure and the use of blood pressure–lowering treatment during the first 24 hours were associated with a reduced risk of poor outcome at 6 months (odds ratio, 0.93; 95% confidence interval, 0.89–0.97; P=0.001 and odds ratio, 0.78; 95% confidence interval, 0.65–0.93; P=0.007, respectively), irrespective of whether the patient was given recombinant tissue-type plasminogen activator (P values for interaction >0.05).

**Conclusions**—Among patients with ischemic stroke who are candidates for thrombolytic treatment, high baseline blood pressure and a large pressure variability during the first 24 hours may be associated with a poor prognosis, whereas a large reduction in blood pressure and the use of blood pressure–lowering treatment during the first 24 hours may be associated with a favorable prognosis. These data support the rationale for further trials of agents that lower blood pressure or reduce blood pressure variability in the acute phase of ischemic stroke.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00120003.

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**Key Words:** antihypertensive agents ▫ blood pressure ▫ cerebral hemorrhage ▫ cerebral infarction ▫ hypertension ▫ stroke ▫ thrombolytic therapy

During the first few hours of ischemic stroke, a high blood pressure or a highly variable blood pressure is often a cause of concern and a common reason for withholding thrombolytic treatment.1,2 High blood pressure around the time of thrombolytic treatment carries an increased risk of intracerebral hemorrhage (in the range of a 4-fold increased risk for a systolic blood pressure >170 compared with 141–150 mm Hg),1,2 and the same may be true for an abrupt increase in
systolic pressure during or shortly after infusion of thrombolytic drugs. However, the prognostic effect of different blood pressure profiles in this situation is unclear, and the Food and Drug Administration labeling for alteplase has recently changed to remove strict upper blood pressure limits for beginning thrombolytic treatment. At the same time, guidelines recommend a conservative approach, with careful blood pressure lowering to a systolic pressure of 185 and a diastolic pressure of 110 mm Hg before the start of thrombolytic treatment and maintenance of a pressure <180/110 mm Hg, but we also know little about the effects of blood pressure–lowering treatment in patients with ischemic stroke given thrombolytic treatment.

Early blood pressure–lowering treatment seems to be beneficial in patients with hemorrhagic stroke, but there has been no clinical trial of blood pressure–lowering treatment focusing only on the first few hours of ischemic stroke. A subgroup analysis of the Efficacy of Nitric Oxide in Stroke (ENOS) trial indicated that blood pressure–lowering treatment is beneficial when given during the first 6 hours of stroke onset, but the same has not been found in other trials, and in all these trials, only a small minority of patients were recruited early or given thrombolytic treatment. The Third International Stroke Trial (IST-3) was a large randomized-controlled trial of thrombolytic treatment within 6 hours of onset of ischemic stroke and recorded blood pressures and the use of blood pressure–lowering agents during the first 24 hours. We have used data from IST-3 to perform exploratory analyses of the short- and long-term effects of blood pressure and blood pressure–lowering treatment during the first 24 hours of ischemic stroke in patients randomly allocated to thrombolytic treatment or control.

Methods

The IST-3 was a randomized-controlled trial of recombinant tissue-type plasminogen activator (r-tPA) 0.9 mg/kg versus open control within 6 hours of ischemic stroke in 3035 patients. For a patient to be eligible for the trial, systolic and diastolic blood pressures had to be ≤220 and ≤130 mm Hg, respectively. All patients had a computed tomographic or magnetic resonance imaging brain scan before randomization and a follow-up scan at 24 to 48 hours, and all were treated within an organized system of stroke care. Further details of the protocol, the baseline characteristics, the statistical analysis plan, and the main results have been published previously. Of the 3035 patients recruited, the median age was 81 years (interquartile range, 72–86) and median National Institute of Health Stroke Scale score was 11 (interquartile range, 6–17), and among those allocated to r-tPA, the median time from onset of stroke to randomization was 3.9 hours (interquartile range, 2.9–4.8) and to the start of treatment was 4.2 hours (interquartile range, 3.2 to 5.2).

Blood pressure was measured according to local protocols and was recorded for trial purposes at 5 time points: at randomization, at the start of treatment (or, for patients allocated open control, immediately after randomization), and at 30 minutes and 1 and 24 hours thereafter. For the purpose of this analysis, we characterized blood pressure by the systolic blood pressure at baseline, the variability of systolic blood pressure (expressed both by the standard deviation (SD) and the range between the lowest and the highest pressures), and the change in systolic blood pressure from baseline to 24 hours. Baseline blood pressure was defined as the highest of the 2 initial blood pressures measured (at randomization and at the start of treatment), and patients contributed to the analysis of blood pressure variability if they had at least 1 postbaseline measurement taken. We chose to use systolic pressure because diastolic blood pressure variability has been shown to be less important, and we chose SD and range as measures of blood pressure variability because they are simple and meaningful for clinical practice and as good as other, more complex measures in predicting outcome. We also recorded the use of blood pressure–lowering treatment during the first 24 hours. The IST-3 protocol specified that patients allocated r-tPA and control must be managed according to local protocols, and in the same clinical environment, but given the lack of reliable data, the protocol did not specify any blood pressure management regimen.

Adverse events occurring during hospitalization up to the first 7 days of stroke were recorded on case report forms and adjudicated centrally by reviewers who were blinded to treatment allocation. Functional outcome at 6 months was scored with the Oxford Handicap Scale, which is a commonly used variant of the modified Rankin Scale, either by a postal questionnaire mailed to the patient or telephone interview by personnel who were blinded to treatment allocation. For the present analysis, we have selected the following adverse events (nonfatal or fatal) occurring during the first 7 days: symptomatic swelling of the original infarct, symptomatic intracranial hemorrhage (ICH), neurological deterioration (defined as a relevant clinical deterioration) not due to swelling or ICH, early recurrent ischemic stroke, and any early adverse event (all of the above, plus deaths from noncerebral causes). In addition, we analyzed effects on deaths from all causes within 7 days and on functional outcome at 6 months, categorized as good (Oxford Handicap Scale scores, 0 to 2) or poor (scores, 3 to 6).

The purpose of the analyses was to examine the effects of blood pressure and blood pressure–lowering treatment on the whole range of early cerebral adverse events, early deaths, and late functional outcome, in agreement with the protocol and the statistical analysis plan. Our interest was in the pattern of effects rather than the effect on a particular primary effect variable, and therefore, we performed crude analyses of overall effects, rather than analyses of gradient effects. The associations between the blood pressure variables or blood pressure–lowering treatment (independent variables) and early adverse events and functional outcome at 6 months (dependent variables) were tested with logistic regression, with adjustment for the following prespecified key variables: age, National Institute of Health Stroke Scale score, time to randomization, and allocated treatment (r-tPA or control). Systolic blood pressure at randomization was also adjusted for in the analyses of blood pressure variability, and for the analyses of variability, we also performed a sensitivity analysis using only the 4 measurements taken ≤1 hour after the start of treatment. The associations between blood pressure variables and whether blood pressure–lowering treatment was given were similarly assessed, adjusting for the same variables. To test for interactions with treatment (r-tPA or control) in each of the adjusted models for the effect of an individual blood pressure variable or blood pressure–lowering treatment, we added a single interaction term. As well as testing whether the interaction was nominally significant, we examined the treatment-specific effects in these adjusted models to identify any consistency of differences between r-tPA and control. Finally, we tested whether there was any interaction with timing of r-tPA treatment (<4.5 or ≥4.5 hours after symptom onset) or persistence of arterial occlusion (the presence of the hyperdense cerebral artery sign on noncontrast computed tomographic or magnetic resonance imaging). We used a nominal P value of 0.05 as a threshold for statistical significance, but tests were multiple and exploratory and must therefore be regarded with caution. Analyses were done with SAS (version 9.3).

Results

Of the 3035 patients included in the trial, 3028 (99.9%) contributed to the analysis of baseline systolic blood pressure, 3018 (99.6%) to SD, 3028 (99.9%) to range, 2926 (96.5%) to change in systolic blood pressure, and 3028 (99.9%) to analysis of blood pressure–lowering treatment. Systolic blood pressures were similar in patients allocated to thrombolytic treatment and control (P > 0.05; Figure 1). Median systolic
pressures were 155 and 156 mm Hg in the 2 groups at baseline and were lower by ≈10 mm Hg in both groups at 24 hours after the start of treatment.

Effects of Blood Pressure on Early Adverse Events and Poor Functional Outcome at 6 Months

The Table shows the baseline characteristics of patients in the trial, with respect to systolic blood pressure at baseline, SD of systolic blood pressure, range of systolic blood pressure, and change in systolic blood pressure during the first 24 hours. There was a larger change in blood pressure among patients allocated to thrombolytic treatment, but there was otherwise no statistically significant difference between patients allocated to thrombolytic treatment and those allocated to control, and no clinically important differences in other characteristics, for example, time to randomization, age, or stroke severity.

Figure 2 shows baseline systolic blood pressure in patients with or without early adverse events, early death, and poor functional outcome at 6 months. Patients who experienced any of the early adverse events during the first 7 days had higher baseline systolic blood pressure than others (mean 162 versus 159 mm Hg; P value from logistic regression analysis=0.016). Although we observed a higher blood pressure for each individual type of adverse event, this reached the threshold for statistical significance only for symptomatic ICH (mean 165 versus 159 mm Hg; P=0.015), and the odds of symptomatic ICH were estimated to increase by 10% (95% confidence interval [CI], 2–19) for each 10-mm increase in baseline systolic blood pressure.

The effects of blood pressure variability, expressed as the SD of systolic blood pressure, are shown in Figure 3. We observed a greater SD for patients experiencing any early adverse event (mean 14.7 versus 13.4 mm Hg; P=0.003), although this did not reach statistical significance for any individual type of event apart from early death (15.4 versus 13.5 mm Hg; P=0.001). The odds of early death were estimated to be 36% higher (95% CI, 15–61) for a 10-mm increase in SD. This pattern was similar when blood pressure variability was expressed as the range of systolic blood pressures, which was also higher in patients with any early adverse event or early death (P=0.002 and P=0.003, respectively; Figure I in the online-only Data Supplement). We also performed sensitivity analyses of blood pressure variability using only the 4 measurements taken ≤1 hour after the start of treatment and found similar results for both SD and range of systolic blood pressure (data not shown).

A large decline in systolic blood pressure during the first 24 hours generally showed the opposite associations, with lower risks (Figure 4). Patients with a larger decline had a small, statistically nonsignificant higher risk of early recurrent ischemic stroke but a lower risk of the other events, and for symptomatic ICH and poor outcome at 6 months, the differences were statistically significant (mean 12.3 versus 14.2 mm Hg; P=0.037 and 12.2 versus 17.5 mm Hg; P=0.001, respectively). For each 10-mm increase in blood pressure decline, the odds of symptomatic ICH and poor outcome at 6 months were estimated to reduce by 10% (95% CI, 1–18) and 7% (95% CI, 3–11), respectively.

Finally, we performed an interaction analysis to see if the effects were different in the r-tPA group and the control group, in patients treated before and after 4.5 hours of symptom onset, and patients with and without the hyperdense cerebral artery sign and found no evidence of such differences, for any of the early adverse events, early deaths, or poor functional outcome at 6 months (P values for interaction>0.05, data not shown).

Effects of Blood Pressure–Lowering Treatment on Early Adverse Events and Poor Functional Outcome at 6 Months

The Table shows the baseline characteristics in patients who received blood pressure–lowering treatment during the first 24
hours after the start of thrombolytic treatment or control. The proportion of patients who was given blood pressure–lowering treatment was about the same in the r-tPA (35.6%) and control (38.3%) groups, and again there were no important differences between other patient subgroups.

We compared the blood pressure characteristics in patients who received and patients who did not receive blood pressure–lowering treatment during the first 24 hours. As expected, patients who received treatment had higher blood pressure at baseline, higher blood pressure variability, and a larger decline by 24 hours (Table I in the online-only Data Supplement).

Figure 5 shows the associations between blood pressure–lowering treatment during the first 24 hours and early adverse events, early deaths, and poor outcome at 6 months. Blood pressure–lowering treatment was not associated with any change in the risk of neurological deterioration and early recurrent ischemic stroke, but with lower risks of the other early adverse events, early deaths, or poor functional outcome at 6 months ($P$ values for interaction>0.05, data not shown). Figure II in the online-only Data Supplement shows the effect of blood pressure–lowering treatment on functional outcome in these subgroups.

### Discussion

A high systolic blood pressure or a highly variable blood pressure is often a reason for withholding thrombolytic treatment, mainly because of the fear of ICH. The present analyses suggest that these blood pressure characteristics are associated not only with an increased risk of symptomatic ICH but also with other cerebral adverse events, early death, and poor functional outcome at 6 months. Only some of the risk increases were statistically significant, but nearly all risk estimates pointed in the same direction and lend support to the hypothesis that blood pressure is not an innocent bystander but a player that can have a direct effect on the natural course of ischemic stroke.

It has previously been shown that high blood pressure in the acute phase has an unfavorable effect on outcome. Blood pressure variability is another blood pressure characteristic,

| Table. Baseline Characteristics of Patients Described by BP or by BP-Lowering Treatment During the First 24 Hours |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Age, y                                          | SBP at Baseline                                 | SD of SBP                                      | Range of SBP                                    | Change in SBP                                   |
| n                                              | Mean   | SD    | Mean   | SD    | Mean   | SD    | Mean   | SD    |
| ≤80                                            | 1413   | 157.2 | 23.7   | 13.0   | 7.1    | 31.1  | 17.4   | 13.2   | 22.3  | 511 (36.2) |
| >80                                            | 1615   | 161.6 | 23.5   | 14.3   | 7.5    | 34.2  | 18.5   | 15.0   | 24.8  | 608 (37.6) |
| Sex                                            |        |       |       |       |        |       |       |       |       |       |
| Female                                         | 1567   | 160.7 | 24.3   | 14.1   | 7.5    | 33.7  | 18.4   | 13.5   | 24.3  | 594 (37.9) |
| Male                                           | 1461   | 158.4 | 23.0   | 13.3   | 7.2    | 31.7  | 17.6   | 14.8   | 23.1  | 525 (35.9) |
| Treatment arm                                  |        |       |       |       |        |       |       |       |       |       |
| r-tPA                                          | 1513   | 160.4 | 23.4   | 14.0   | 7.4    | 33.9  | 18.3   | 15.9   | 23.5  | 538 (35.6) |
| Control                                        | 1515   | 158.8 | 23.9   | 13.4   | 7.4    | 31.5  | 17.7   | 12.4   | 23.8  | 581 (38.3) |
| Time to treatment, h                           |        |       |       |       |        |       |       |       |       |       |
| ≤3                                             | 847    | 161.5 | 24.0   | 14.3   | 7.3    | 34.2  | 18.0   | 15.1   | 24.2  | 331 (39.1) |
| >3                                             | 2179   | 158.8 | 23.5   | 13.5   | 7.4    | 32.2  | 18.1   | 13.8   | 23.5  | 788 (36.2) |
| NIHSS score                                    |        |       |       |       |        |       |       |       |       |       |
| ≤10                                            | 1461   | 160.5 | 23.4   | 13.7   | 7.1    | 32.6  | 17.6   | 17.5   | 22.6  | 597 (40.9) |
| >10                                            | 1567   | 158.8 | 23.9   | 13.8   | 7.6    | 32.8  | 18.5   | 10.9   | 24.3  | 522 (33.3) |
| Stroke subtype                                 |        |       |       |       |        |       |       |       |       |       |
| TACI                                           | 1302   | 159.7 | 24.2   | 13.8   | 7.5    | 32.9  | 18.3   | 11.2   | 24.0  | 424 (32.6) |
| PACI                                           | 1145   | 159.3 | 23.0   | 13.8   | 7.2    | 33.0  | 17.8   | 16.1   | 23.5  | 470 (41.0) |
| LACI                                           | 332    | 159.7 | 25.6   | 13.1   | 7.8    | 31.4  | 18.4   | 16.0   | 22.6  | 136 (40.9) |
| POCI                                           | 244    | 159.8 | 21.0   | 13.5   | 6.9    | 32.5  | 17.1   | 17.8   | 23.4  | 86 (35.2) |
| Infarct size                                   |        |       |       |       |        |       |       |       |       |       |
| No infarct visible                             | 1801   | 160.6 | 23.7   | 13.9   | 7.4    | 33.0  | 18.1   | 15.5   | 23.7  | 716 (39.8) |
| Small/medium                                   | 695    | 158.8 | 23.5   | 13.3   | 7.4    | 31.9  | 17.9   | 14.1   | 23.6  | 240 (34.5) |
| Large/very large                               | 515    | 157.3 | 23.9   | 13.7   | 7.3    | 33.0  | 18.1   | 9.7    | 23.6  | 158 (30.7) |

BP indicates blood pressure; NIHSS, National Institute of Health Stroke Scale; LACI, lacunar infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; r-tPA, recombinant tissue-type plasminogen activator; SBP, systolic blood pressure; and TACI, total anterior circulation infarct.
which expresses the tendency of blood pressure to change abruptly around the mean pressure. Blood pressure variability has been shown to be an independent risk factor for stroke\textsuperscript{12} and to have prognostic significance in the acute phase of ICH\textsuperscript{13,17} but there are only limited data to support the notion that the same is true during the first few hours of ischemic stroke.\textsuperscript{18–21} Our data confirm and extend these findings in a much larger prospectively and carefully studied cohort. It may

\begin{figure}
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\caption{Associations of systolic blood pressure at baseline. Columns represent mean±1 standard error. Odds ratios (ORs), 95\% confidence intervals (CIs), and $P$ values are from logistic regression analyses of 10-mm Hg increments, adjusted for key clinical variables (see text). Only $P$ values <0.05 are given. ICH indicates intracranial hemorrhage; and ND, neurological deterioration.}
\end{figure}

\begin{figure}
\begin{center}
\includegraphics[width=\textwidth]{figure3.png}
\end{center}
\caption{Associations of SD of systolic blood pressure. Columns represent mean±1 standard error. Odds ratios (ORs), 95\% confidence intervals (CIs), and $P$ values are from logistic regression analyses of 10-mm Hg increments, adjusted for key clinical variables (see text). Only $P$ values <0.05 are given. SD was missing for 15 cases, among whom 1 had early death and 11 had poor outcome at 6 months. ICH indicates intracranial hemorrhage; and ND, neurological deterioration.}
\end{figure}
be that, during the early stages of ischemic stroke, the brain is vulnerable to changes in blood pressure, perhaps both because of a disturbed cerebral arterial autoregulation and because of the breakdown of the arterial wall at the site of infarction. A high blood pressure, or abrupt increases in blood pressure, may cause raised intracranial pressure and edema or bleeding at the site of infarction and consequently lead to death or poor functional outcome in the longer term, as indicated by our analysis.

Compatible with this pathophysiological theory, we also observed a pattern in which a larger decline in blood pressure during the first 24 hours was (nonsignificantly) associated with lower risks of symptomatic infarct swelling, symptomatic ICH, and neurological deterioration from other causes but not with a lower risk of recurrent ischemic stroke. The somewhat higher frequency of recurrent ischemic strokes in patients with a larger fall in blood pressure may theoretically be explained

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**Figure 4.** Associations of change in systolic blood pressure. Columns represent mean±1 standard error. Odds ratios (ORs), 95% confidence intervals (CIs), and P values are from logistic regression analyses of 10-mm Hg increments, adjusted for key clinical variables (see text). Only P values <0.05 are given. Systolic blood pressure at 24 hours was missing for 102 cases. Among these 10, 18, 11, 0, 47, 45, and 82, respectively, experienced the 7 types of outcome shown. ICH indicates intracranial hemorrhage; and ND, neurological deterioration.

**Figure 5.** Associations of blood pressure (BP)–lowering treatment. Columns represent mean±1 standard error. Odds ratios (ORs), 95% confidence intervals (CIs), and P values are from logistic regression analyses adjusted for key clinical variables (see text). Only P values <0.05 are given. ICH indicates intracranial hemorrhage; and ND, neurological deterioration.
by a critically low perfusion pressure in some patients because of the disruption of cerebral arterial autoregulation. However, the favorable effects of a larger fall in blood pressure on the other types of early adverse events possibly outweighed the effect on recurrent ischemic strokes, which may explain the significant positive effect on functional outcome at 6 months.

As could be expected from the unfavorable effects of high baseline blood pressure and large pressure variability and the favorable effects of an early decline in blood pressure, we observed that early blood pressure–lowering treatment was associated with a reduced number of most types of early adverse events and with a reduced risk of poor outcome at 6 months. Interestingly, we observed a small increase in the number of recurrent ischemic strokes, as in patients with a large decline in blood pressure. Taken together, these findings support the hypothesis that early blood pressure treatment may be beneficial during the first few hours of ischemic stroke, as in hemorrhagic stroke and as suggested by the ENOS subgroup analysis. In previous trials of blood pressure–lowering treatment after ischemic stroke, blood pressure–lowering treatment has on average been started after 24 hours, which may explain why, overall, no beneficial effects could be observed. One small trial of blood pressure–lowering treatment given in the ambulance within 4 hours of stroke onset has shown promising results, and the Second Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT-2) is now starting (Philipp Bath, personal communication).

Importantly, the present analyses show that the results seem to apply irrespective of whether patients are treated with r-tPA and irrespective of whether patients were treated before or after 4.5 hours of symptom onset. This means that, if our results can be confirmed, blood pressure–lowering treatment during the first few hours can be safely applied to patients who are candidates for thrombolytic treatment and suggests that the current recommendations may be too conservative. The Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) of blood pressure–lowering treatment in patients given thrombolytic treatment is ongoing, and our results strengthen the rationale for this trial. The analyses also indicate that the results apply irrespective of whether patients had evidence of persistent arterial occlusion, but this does not exclude the possibility that the effect of blood pressure–lowering treatment vary by subtype of stroke, for example, stroke because of large-artery occlusion or stenosis or by differing degrees of collateral artery flow.

The present analyses have clear limitations, and the findings must be interpreted with caution. First, IST-3 did not randomly allocate patients to blood pressure treatment or control, and so, our data are observational and prone to confounding and bias. We have controlled in the analyses for many key prognostic variables, but we may not have been able to control for them all, which means that patients receiving blood pressure–lowering treatment may differ from other patients in many respects (confounding by indication). Similarly, patients with an unfavorable blood pressure profile may differ from other patients. It is also a possibility that blood pressure is a marker of a poor prognosis, rather than a cause (reverse causality), and therefore, it is difficult to draw firm conclusions about the effects of blood pressure characteristics and blood pressure–lowering treatment, based on our analyses. Second, the multiple exposure variables used in the present analyses are related, which means that the results must also be seen as related. Third, blood pressure in IST-3 was not measured uniformly by a standardized, validated blood pressure monitor. However, this would have reduced the statistical noise and increased the precision of the blood pressure readings, thereby likely increasing the statistical significance of our findings. Furthermore, because our estimate of blood pressure variability was based on a relatively low number of measurements, we might further have underestimated the true significance of blood pressure variability because the precision of the risk estimate is heavily dependent on the number of measurements. Fourth, IST-3 did not collect detailed information about the blood pressure–lowering treatment that was given, which makes it impossible to determine whether the observed effects were restricted to certain types or doses of drugs or to a certain timing of treatment. Fifth, the trial was not powered to detect statistically significant risk differences resulting from change in blood pressure or from blood pressure–lowering treatment, and therefore, it is a possibility that the observed differences are falsely positive because of the play of chance. Also, we have performed multiple tests, which increases the risk of spurious findings. However, all risk differences were internally consistent and biologically plausible, and for functional outcome at 6 months, the effect variable with the largest statistical power, the difference was highly statistically significant.

The main strengths of this analysis are that IST-3 was a large study of patients with early ischemic stroke given thrombolytic treatment, with blood pressure measured at fixed intervals according to a standardized protocol, including many patients who received blood pressure–lowering treatment. Adverse events were adjudicated centrally and blindly, and recording of 6-month outcome was near complete and was done without recall of blood pressure and blood pressure–lowering treatment in the acute phase, which reduces the possibilities of bias. The study population was also well characterized and shares many characteristics with patients who are admitted early and given thrombolytic treatment in a general hospital setting. In the absence of any completed large randomized-controlled trial of blood pressure–lowering treatment during the first hours of ischemic stroke, we think that IST-3 offers a good opportunity to assess the effects of blood pressure characteristics and blood pressure–lowering treatment in such patients.

In summary, among patients with ischemic stroke who are candidates for thrombolytic treatment, blood pressure characteristics and blood pressure–lowering treatment during the first 24 hours seem to have important effects on short- and long-term prognosis. Higher baseline systolic blood pressure and larger blood pressure variability were associated with a poorer prognosis, whereas an early decline in blood pressure and blood pressure–lowering treatment given during the first 24 hours were both associated with a favorable prognosis. These findings lend weight to the importance of blood pressure after ischemic stroke and indicate that early changes in
blood pressure may be of greater importance than previously considered. The findings also support that agents that lower blood pressure or reduce pressure variability should be tested further in the hyperacute phase of ischemic stroke to determine whether current guidelines for management of blood pressure in this situation are too conservative.

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E. Berge wrote the first draft of the report. G. Cohen performed the analyses and commented on the report. R.I. Lindley, J.M. Wardlaw, and P. Sandercock were co-chief investigators in the IST-3 and commented on the report. E.C. Sandset and W. Whiteley commented on the report.

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Disclosures

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References


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Supplemental Material

Supplemental Figure I. Associations of range of systolic blood pressure

Columns represent means +/- 1 standard error. ORs, 95% CIs and p-values are from logistic regression analyses of 10 mm Hg increments, adjusted for key clinical variables (see text). Only p-values <0.05 are given. Range was missing for 5 cases, among whom 1 had early death and 4 had poor outcome at 6 months. ICH intracerebral haemorrhage; ND neurological deterioration.
**Supplemental Table I.** Blood pressure characteristics in patients given or not given blood pressure lowering treatment during the first 24 hours

<table>
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<tr>
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<th>No BP lowering treatment (N=1909)</th>
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<td>Mean</td>
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<tr>
<td>SBP at randomisation</td>
<td>159.7</td>
<td>24.0</td>
<td>152.5</td>
</tr>
<tr>
<td>SBP at start of treatment</td>
<td>159.6</td>
<td>24.0</td>
<td>151.5</td>
</tr>
<tr>
<td>SBP at 30 minutes</td>
<td>157.6</td>
<td>25.5</td>
<td>150.1</td>
</tr>
<tr>
<td>SBP at 1 hour</td>
<td>155.3</td>
<td>25.4</td>
<td>147.9</td>
</tr>
<tr>
<td>SBP at 24 hours</td>
<td>147.8</td>
<td>23.9</td>
<td>144.1</td>
</tr>
<tr>
<td>Standard deviation of SBP</td>
<td>14.3</td>
<td>7.6</td>
<td>13.4</td>
</tr>
<tr>
<td>Range of SBP</td>
<td>34.3</td>
<td>18.8</td>
<td>31.8</td>
</tr>
<tr>
<td>Change in SBP</td>
<td>-16.6</td>
<td>24.0</td>
<td>-12.6</td>
</tr>
</tbody>
</table>

SBP systolic blood pressure (mm Hg)

¹Adjustment for linear effects of age, NIHSS score, delay time and allocated treatment (rt-PA or control)
**Supplemental Figure II.** Effects of blood pressure lowering treatment on functional outcome in important subgroups

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rt-PA treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.78 (0.60-1.01)</td>
<td>0.94</td>
</tr>
<tr>
<td>No</td>
<td>0.77 (0.60-0.99)</td>
<td></td>
</tr>
<tr>
<td><strong>Time to treatment (hours)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4.5</td>
<td>0.77 (0.61-0.96)</td>
<td>0.85</td>
</tr>
<tr>
<td>≥4.5</td>
<td>0.79 (0.59-1.10)</td>
<td></td>
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<tr>
<td><strong>Vascular occlusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.78 (0.51-1.21)</td>
<td>0.95</td>
</tr>
<tr>
<td>No</td>
<td>0.77 (0.63-0.95)</td>
<td></td>
</tr>
</tbody>
</table>

CI confidence interval; OR odds ratio; Rt-PA recombinant tissue plasminogen activator
急性虚血性脳卒中の血栓溶解療法に関する Third International Stroke 試験の被験者における発症後 24 時間以内の血圧と血圧降下薬の影響

Effects of Blood Pressure and Blood Pressure-Lowering Treatment During the First 24 Hours Among Patients in the Third International Stroke Trial of Thrombolytic Treatment for Acute Ischemic Stroke

Eivind Berge, MD; Geoffrey Cohen, MSc; Richard I. Lindley, MD, et al.

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Stroke 2015; 46: 3362-3369. DOI: 10.1161/STROKEAHA.115.010319.
급성허혈뇌졸중 환자에 대한 Third International Stroke Trial of Thrombolytic Treatment에서 초기 24시간 동안의 혈압과 혈압강하치료에 대한 효과

Effects of Blood Pressure and Blood Pressure–Lowering Treatment During the First 24 Hours Among Patients in the Third International Stroke Trial of Thrombolytic Treatment for Acute Ischemic Stroke

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(Stroke. 2015;46:3362-3369.)

Key Words: antihypertensive agents ■ blood pressure ■ cerebral hemorrhage ■ cerebral infarction ■ hypertension ■ stroke ■ thrombolytic therapy

배경과 목적
급성허혈뇌졸중 환자에서 고혈압 혹은 높은 혈압변동성은 혈전 용해치료를 보류하는 흔한 원인이나, 진료지침에서는 이러한 상황에서 적극적인 혈압강하에 대해서는 보존적인 접근을 추천하고 있다. 저자들은 급성허혈뇌졸중의 혈전용해 치료에 대한 무작위 환자대조군 연구에 포함되어 있는 환자들에서 혈압과 혈압강하치료의 임상적인 효과에 대한 탐색적 분석을 진행하였다.

방법
The Third International Stroke Trial (IST–3) 연구에서는 증상 발생 6시간 이내의 3035명의 허혈뇌졸중 환자들을 0.9 mg/kg 용량의 조직플라스미노게네이저 투여군과 공개 대조군으로 무작위 배정하였다. 혈압은 무작위 배정 시, 치료 시작 시, 치료 시작 이후 30분, 1시간 및 24시간 이후에 측정되었고, 초기 24시간 동안의 혈압강하치료 방법을 기록하였다. 혈압 지표는 기저 수축기 혈압의 평균, 수축기 혈압 변동성(표준편차 및 제일 높은 혈압과 제일 낮은 혈압의 차이), 기저시점에서 24시간 시점의 수축기 변 화로 정의하였다. 저자들은 로지스틱회귀분석을 통하여 주요 예 후관련 인자를 보정한 후 혈압 지표 혹은 혈압강하치료가 조기 유해사건, 조기 사망 혹은 6개월 이후의 기능적 예후와 관련이 있는지 조사하였다.

결과
초기 24시간 이내의 높은 혈압 혹은 높은 혈압변동성은 여러 통 hazard ratio, 0.59; 95% confidence interval, 0.35–0.93; P=0.03)는 PAF에서 뇌졸중, 전신색전증, 모든 원인의 사망의 복 합결과가 더 낮았는데 이는, OAC 사용자(hazard ratio, 0.77; 95% confidence interval, 0.59–0.99; P=0.046)와 OAC 비사 용자(hazard ratio, 0.59; 95% confidence interval, 0.46–0.75; P<0.01)에서 모두 그러하였다. 다변량분석에서 PAF는 뇌졸중 및 전신색전증의 낮은 발생률의 독립적인 예측인자였다.
계적 방법을 통하여 초기유해사건 및 초기 사망의 발생과 관련이 있었으며 통계적으로 유의하였다. 초기 24시간 이내에 혈압의 감소가 크고(OR, 0.93; 95% CI, 0.89–0.97; P=0.001) 혈압강하치료제를 사용한 경우(OR, 0.78; 95% CI, 0.65–0.93; P=0.007) 환자들이 조직플라스미노강화효과의 투여 여부와는 상관없이(상호작용에 대한 P>0.05) 6개월째의 불량한 예후의 위험 감소와 관련이 있었다.

**결론**
혈전용해치료를 할 가능성이 높은 급성뇌졸중 환자에서 초기 24시간 이내의 높은 초기 혈압 및 높은 혈압변동성은 불량한 예후와 관련이 될 수 있으며, 반면 초기 24시간 동안의 혈압의 감소가 크거나 혈압강하치료를 사용한 경우에는 양호한 예후와 관련이 있었다. 이러한 결과는 혈압를 조절할 필요가 있는 약제들에 대한 추가적인 임상연구들에 대한 근거를 뒷받침한다.

**Figure 3.** Associations of SD of systolic blood pressure. Columns represent mean±1 standard error. Odds ratios (ORs), 95% confidence intervals (CIs), and P values are from logistic regression analyses of 10-mm Hg increments, adjusted for key clinical variables (see text). Only P values <0.05 are given. SD was missing for 15 cases, among whom 1 had early death and 11 had poor outcome at 6 months. ICH indicates intracranial hemorrhage; and ND, neurological deterioration.clinical variables (see text). Only P values <0.05 are given. ICH indicates intracranial hemorrhage; and ND, neurological deterioration.

**Figure 4.** Associations of change in systolic blood pressure. Columns represent mean±1 standard error. Odds ratios (ORs), 95% confidence intervals (CIs), and P values are from logistic regression analyses of 10-mm Hg increments, adjusted for key clinical variables (see text). Only P values <0.05 are given. Systolic blood pressure at 24 hours was missing for 102 cases. Among these 10, 18, 11, 0, 47, 45, and 82, respectively, experienced the 7 types of outcome shown. ICH indicates intracranial hemorrhage; and ND, neurological deterioration.

**Figure 5.** Associations of blood pressure (BP)-lowering treatment. Columns represent mean±1 standard error. Odds ratios (ORs), 95% confidence intervals (CIs), and P values are from logistic regression analyses adjusted for key clinical variables (see text). Only P values <0.05 are given. ICH indicates intracranial hemorrhage; and ND, neurological deterioration.