Hypertension and Its Treatment in the NINDS rt-PA Stroke Trial

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Background and Purpose—We examined the frequency, course, and treatment of hypertension in the NINDS rt-PA Stroke Trial.

Methods—Blood pressure (BP) was measured at the time of admission, at randomization, and then 36 times during the first 24 hours after randomization. Patients with a systolic BP of >185 mm Hg and a diastolic BP of >110 mm Hg at admission were defined as hypertensive before randomization, and those with a systolic BP of >180 mm Hg or a diastolic BP of >105 mm Hg within the first 24 hours after randomization were defined as hypertensive after randomization. Standardized clinical assessments were conducted at 24 hours and at 3 months. Post hoc analyses were conducted to evaluate the association of antihypertensive therapy with clinical outcomes.

Results—Of the 624 patients, 121 (19%) had hypertension on admission and 372 (60%) had hypertension in the 24 hours after randomization. The use of antihypertensive therapy before randomization (tPA 9%, placebo 9%) and after randomization (tPA 24%, placebo 29%) was similar between placebo- and tPA-treated patients. No adverse effects of prerandomization antihypertensive therapy on 3-month favorable outcome were detected for either the placebo- or tPA-treated groups. For placebo patients with hypertension in the 24 hours after randomization, clinical outcome measures were similar for those patients who did and did not receive antihypertensive therapy after randomization ($P=0.26$); antihypertensive therapy was not associated with declines in BP ($P=0.44$) or with abrupt declines ($P=0.14$). Those tPA patients who were hypertensive after randomization and received antihypertensive therapy were less likely to have a favorable outcome at 3 months ($P<0.01$) than those who were hypertensive and did not receive antihypertensive therapy.

Conclusions—The frequency of hypertension and the use of antihypertensive therapy were similar between the tPA and placebo groups in the NINDS rt-PA Stroke Trial. In the placebo group, antihypertensive therapy was not associated with less favorable outcomes at 3 months; postrandomization antihypertensive therapy was associated with less favorable outcomes for the tPA patients who were hypertensive. However, because of the nonrandomized use of antihypertensive therapy and the many post hoc comparisons leading to type 1 errors, the significance of this observation is unclear. Careful attention to BP and gentle management remain warranted for stroke patients treated with tPA. (Stroke. 1998;29:1504-1509.)

Key Words: blood pressure ■ clinical trials ■ hypertension ■ plasminogen activator, tissue type ■ stroke

Hypertension is a frequent finding in the first hours following onset of acute ischemic stroke.1 Systolic blood pressures (BPs) exceeding 160 mm Hg or diastolic BPs exceeding 90 mm Hg may be found in 35% or more patients examined in the first minutes after symptom onset.1 Current treatment guidelines suggest that elevated arterial pressures should not be treated unless the systolic BP exceeds 200 to 210 mm Hg or the diastolic BP exceeds 120 mm Hg.2-4 These guidelines are supported by studies5 of cerebral blood flow

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Drs Frankel, Kwiatkowski, Kothari, and Haley are on the Genentech Speakers Bureau and receive honoraria.

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suggesting loss of autoregulation within regions of acutely ischemic brain such that falls in arterial pressure and perfusion could amplify ischemia in the core and penumbra of an evolving cerebral infarct. Despite rationale for caution, firm clinical evidence for or against the use of antihypertensive therapy from randomized trials is not available. Furthermore, while abrupt substantial declines in mean arterial pressure have been shown to reduce cerebral blood flow, the threshold below which it is unsafe to lower mean arterial pressure is unknown.6

In the design of the dose-finding safety trial of recombinant tissue plasminogen activator,7,8 the risk of symptomatic brain hemorrhage (ICH) was anticipated and the potential link of ICH to elevation in BP was recognized. BP eligibility criteria more stringent than those used for tPA-treatment of acute myocardial infarction were instituted, but aggressive measures to lower BP to allow enrollment were prohibited to prevent precipitous falls in BP. After initiation of tPA therapy, a BP management algorithm was followed, adapted from a similar algorithm designed for treatment of stroke patients in general.9 Recommended drugs were selected because of their rapid onset of action and because of their predictable effects with low potential for overshoot.10 Adjustments in the algorithm were made in response to experience during the course of the trial.

In the NINDS rt-PA Stroke Trial,11 the investigators chose BP eligibility criteria similar to those used in the dose-finding trial. The BP management algorithm from the dose-finding trial was used because of the low incidence of symptomatic ICH in the pilot study7,8 and the relationship of ICH in that study to elevations in diastolic BP.12 We now examine the frequency, course, and treatment of hypertension in the NINDS study and assesses differences between placebo-treated patients and tPA-treated patients, including assessment of differences in clinical outcomes related to the treatment of BP.

### Subjects and Methods

All patients had BP measurements at the time of admission to the emergency department and at the time of randomization (equivalent to the time of study-drug initiation). Those with a systolic BP of ≤185 mm Hg and a diastolic BP of ≤110 mm were eligible for randomization. Patients with higher BP readings at the time of admission but who met BP criteria by the time of randomization were defined as use of intravenous nitroprusside or repeated intravenous infusions of other medications, could not be used to meet eligibility criteria. After randomization, BP measurements were collected prospectively on a scheduled basis (Appendix 2). Patients with elevations of systolic BP >180 mm Hg or of diastolic BP >105 mm Hg in the 24 hours after randomization were defined as hypertensive after randomization. For such elevations, repeat BP determinations were recommended every 5 to 10 minutes but were not recorded in the trial. Prespecified antihypertensive treatment guidelines were given (Appendix 2). The date of administration of any antihypertensive treatment was recorded but not the time of administration. Acute antihypertensive therapy was defined as administration of intravenous nitroprusside, nicardipine, labetalol, or hydralazine; sublingual nifedipine; and sustained-released or topical nitroglycerin.

To explore the relationship among BP reduction, thrombolytic therapy, and antihypertensive therapy, the severity of hypertension and declines in BPs were calculated at various time frames from randomization. To evaluate severity of hypertension, for each patient in the study the maximum mean arterial pressure during the first 24 hours after baseline was calculated. To detect a decline in BP that may have occurred any time during the first 24 hours, the maximum decline in mean arterial pressure between the time of randomization and any time during the first 24 hours was calculated. To identify precipitous drops in BP soon after initiation of placebo or tPA, the maximum abrupt decline, defined as the maximum decline between two consecutive mean arterial pressures during the first 8 hours, was calculated (measurements were hourly after the first 8 hours).

To examine the potential impact of antihypertensive therapy on the patient’s clinical symptoms, standardized clinical assessments were conducted at 24 hours and at 3 months after randomization, as defined in our original report.11 Improvement at 24 hours (defined as a 4-point or greater decrease in the National Institutes of Health Stroke Scale [NIHSSS], or complete resolution) and deterioration at 24 hours (defined as a 4-point or greater increase from the baseline NIHSSS) were determined; adverse events, such as ICH and death, were collected as the events occurred. Because randomization of patients into the trial was stratified by center and time (0 to 90 minutes, and 91 to 180 minutes from stroke onset), stratified analyses were conducted where sample size permitted. Prerandomization and postrandomization antihypertensive therapies were evaluated with patients who were hypertensive.

We compared the frequency of antihypertensive therapy between the tPA- and placebo-groups with the Mantel-Haenszel test. We tested the association of antihypertensive therapy with clinical outcomes, including the interaction between antihypertensive therapy and study treatment, with logistic regression, adjusting for baseline covariates imbalance in either tPA or placebo groups between patients receiving or not receiving antihypertensive therapy. These covariates were history of hypertension and history of stroke. An interaction was considered to be present if the P value was ≤0.1. When no interaction was detected, we assumed that the effect of antihypertensive therapy on clinical outcome was the same in either the tPA or the placebo group. When an interaction was detected, this finding implied that the effect of antihypertensive therapy on clinical outcome differs depending on the randomization group (tPA or placebo). Because of the concern for potential negative effects of antihypertensive therapy on placebo-treated patients, we compared effects of antihypertensive therapy within the placebo and tPA groups separately, even in the absence of an interaction. This multiple testing inflates the type 1 error rate. We used global tests13 adjusting for covariates to assess the association of antihypertensive therapy with 3-month favorable outcome for the hypertensive patients. We also tested the association of antihypertensive therapy with BP severity or BP decline. Analyses were also conducted excluding patients with symptomatic ICH within 36 hours.

### TABLE 1. Antihypertensive Therapy by tPA-Treated and Placebo-Treated Groups

<table>
<thead>
<tr>
<th>Hypertension Recorded</th>
<th>Placebo, n</th>
<th>Received Anti-hypertensive Therapy, %</th>
<th>tPA, n</th>
<th>Received Anti-hypertensive Therapy, %</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission†‡</td>
<td>65</td>
<td>34</td>
<td>56</td>
<td>20</td>
<td>0.17</td>
</tr>
<tr>
<td>Within 24 hours after randomization†§</td>
<td>195</td>
<td>41</td>
<td>177</td>
<td>37</td>
<td>0.33</td>
</tr>
<tr>
<td>Not hypertensive by definitions</td>
<td>109</td>
<td>9</td>
<td>127</td>
<td>11</td>
<td>0.81</td>
</tr>
</tbody>
</table>

*Mantel-Haenszel test adjusting for centers and time strata.
†Groups are not mutually exclusive.
‡>185 mm Hg systolic, >110 mm Hg diastolic.
§>180 mm Hg systolic, >105 mm Hg diastolic.
TABLE 2. Associations of Antihypertensive Therapy With Clinical Outcomes for Patients With Hypertension at Admission*

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Placebo (n=65)</th>
<th>tPA (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Antihypertensive Therapy, %</td>
<td>Antihypertensive Therapy, %</td>
</tr>
<tr>
<td>Improvement (+) at 24 hours‡</td>
<td>30/43 (70%)</td>
<td>23/22 (69%)</td>
</tr>
<tr>
<td>Deterioration (−) at 24 hours‡</td>
<td>23/43 (54%)</td>
<td>23/22 (55%)</td>
</tr>
<tr>
<td>Symptomatic ICH &lt;36 hours (−)</td>
<td>0/43</td>
<td>5/22 (23%)</td>
</tr>
<tr>
<td>Death at 3 months</td>
<td>30/65 (46%)</td>
<td>5/56 (9%)</td>
</tr>
<tr>
<td>Favorable outcome at 3 months (+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSSS=0 or 1</td>
<td>19/43 (44%)</td>
<td>9/22 (41%)</td>
</tr>
<tr>
<td>Barthel ≥95</td>
<td>23/43 (54%)</td>
<td>36/22 (93%)</td>
</tr>
<tr>
<td>Rankin=0</td>
<td>19/43 (44%)</td>
<td>18/22 (82%)</td>
</tr>
<tr>
<td>Glasgow=1</td>
<td>21/43 (49%)</td>
<td>27/22 (125%)</td>
</tr>
</tbody>
</table>

*
†Odds ratio (OR) and 95% confidence limits (CI) from Mantel-Haenszel test adjusting for centers and time strata.
‡Improvement at 24 hours defined as decrease in NIHSSS of ≥4 points (or complete resolution) and deterioration defined as ≥4-point increase in NIHSSS.

Results

Hypertension was present on admission for 121 (19%) of the 624 patients eventually randomized into the NINDS rt-PA Stroke Trial; 65 were placebo-treated patients and 56 were tPA-treated patients (Table 1). Postrandomization hypertension was detected during the first 24 hours in 372 patients (60%); 195 were placebo-treated and 177 were tPA patients.

For all patients, the frequency of antihypertensive therapy was similar for both the placebo- and tPA-randomized patients. Before randomization, 28 (9%) of the 312 placebo patients and 28 (9%) of the 312 tPA patients received antihypertensive treatment, whether or not they were hypertensive as defined above; 1 patient in the tPA treated group, included in our analysis, received aggressive antihypertensive therapy (ie, intravenous nitroprusside, a protocol violation). After randomization, 92 placebo patients (29%) and 75 tPA patients (24%) received antihypertensive therapy. Antihypertensive therapy was administered either before or after randomization to 110 placebo patients (35%) and 96 tPA (31%) patients.

Hypertension on Admission and Antihypertensive Therapy Received Before Randomization

Of the 121 patients who were hypertensive on admission, slightly more placebo patients received antihypertensive therapy (22 of 65, 34%) before randomization than did tPA patients (11 of 56, 20%), but the difference was not significant (Table 1). The effects of antihypertensive therapy before randomization were similar in the groups randomized to tPA and placebo for all clinical outcomes except death at 3 months (Table 2).

Hypertension After Randomization and Antihypertensive Therapy Received After Randomization

Of the 372 patients who were hypertensive in the 24 hours after randomization, the frequency of antihypertensive therapy was similar for the placebo and the tPA patients (Table 1, P=0.33). Both tPA and placebo patients who received antihypertensive therapy had a more frequent history of hypertension and a more frequent history of stroke; the groups did not differ significantly by other covariates, including age, stroke severity, and severity of hypertension. Antihypertensive treatment by tPA-placebo interactions were detected, implying that the effect of postrandomization antihypertensive therapy on placebo-treated patients was different from that on tPA-treated patients (Table 3). Excluding patients with symptomatic ICH within 36 hours (20 in tPA and 2 in placebo), the results were similar.

For the 195 placebo patients with postrandomization hypertension, all outcome measures were similar for those patients who received postrandomization antihypertensive therapy compared with those who did not. For tPA patients (with 2 exceptions), those who received antihypertensive therapy did worse in outcomes than tPA patients who did not receive antihypertensive therapy after adjusting for baseline covariates.

Maximum BPs and Declines in BP

For all hypertensive patients, maximum mean arterial pressure within the first 24 hours, maximum abrupt decline, and maximum decline are poorly correlated (correlation coefficient <0.45). The results of BP measurements for placebo- and tPA-treated patients are presented in Table 4.
Patients with more severe BPs were more likely to be treated with antihypertensive therapy regardless of randomization group, placebo or tPA (*P* = 0.03). Table 5 presents the differences, by randomization group, in severity or decline of mean arterial pressure between patients who received antihypertensive therapy and those who did not. Placebo patients treated with antihypertensive therapy were not more likely to have an abrupt decline in BP than those who were not treated. However, tPA patients treated with antihypertensive therapy were more likely to have abrupt decline in BP than those who were not treated (for interaction, *P* < 0.01); after excluding the tPA patients with symptomatic ICH, the interaction persisted (*P* = 0.02).

**TABLE 4.** Mean Arterial Pressure (Severity and Reduction) by Placebo and tPA Groups for Patients Hypertensive After Randomization*

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Placebo (n=195)</th>
<th>tPA (n=177)</th>
<th><em>P</em>†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max indicates maximum.</td>
<td>*Hypertension after randomization defined as systolic BP &gt; 180 mm Hg or diastolic BP &gt; 105 mm Hg within 24 hours after randomization.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max in the first 24 hours, mm Hg</td>
<td>133 (11)</td>
<td>131 (10)</td>
<td>0.15</td>
</tr>
<tr>
<td>Blood pressure decline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max decline from baseline, mm Hg</td>
<td>26 (14)</td>
<td>29 (15)</td>
<td>0.02</td>
</tr>
<tr>
<td>Max abrupt decline, mm Hg</td>
<td>22 (9)</td>
<td>23 (12)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

**Discussion**

This is the first detailed description of hypertension and its treatment within a randomized clinical trial. Hypertension was frequent in the NINDS rt-PA Stroke Trial. At the time of hospital admission, 19% of patients had a BP exceeding 185 mm Hg systolic or 110 mm Hg diastolic. During the first 24 hours after randomization, 60% of patients had a BP exceeding 180 mm Hg systolic or 95 mm Hg diastolic.

**TABLE 5.** Mean Arterial Pressure (Severity and Reduction) by Antihypertensive Therapy for Patients Hypertensive After Randomization*

<table>
<thead>
<tr>
<th>Antihypertensive Therapy</th>
<th>Placebo group</th>
<th>tPA group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization Group</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Placebo</td>
<td>n=80</td>
<td>n=115</td>
</tr>
<tr>
<td>Blood pressure severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max in the first 24 hours, mm Hg</td>
<td>135 (11)</td>
<td>131 (10)</td>
</tr>
<tr>
<td>Blood pressure decline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max decline from baseline, mm Hg</td>
<td>28 (14)</td>
<td>25 (14)</td>
</tr>
<tr>
<td>Max abrupt decline, mm Hg</td>
<td>21 (7)</td>
<td>22 (11)</td>
</tr>
<tr>
<td>IPA group</td>
<td>n=112</td>
<td>n=65</td>
</tr>
<tr>
<td>Blood pressure severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max in the first 24 hours, mm Hg</td>
<td>134 (12)</td>
<td>130 (9)</td>
</tr>
<tr>
<td>Blood pressure decline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max decline from baseline, mm Hg</td>
<td>30 (17)</td>
<td>29 (14)</td>
</tr>
<tr>
<td>Max abrupt decline, mm Hg</td>
<td>26 (14)</td>
<td>22 (9)</td>
</tr>
</tbody>
</table>

*Hypertension after randomization defined as systolic BP > 180 mm Hg or diastolic BP > 105 mm Hg within 24 hours after randomization.†Test adjusting for clinical center, time strata, and baseline covariates imbalanced between patients receiving and not receiving antihypertensive therapy.‡Abrupt decline defined as the maximum decline between 2 consecutive mean arterial pressures during the first 8 hours of randomization.
diastolic. Of note, the placebo- and the tPA-treated patients were similar with regard to the presence of hypertension and with regard to the proportion being treated with antihypertensive therapy.

Protection of the patients randomized to placebo was an explicit concern of the investigators in the design and execution of the trial. Hypertensive placebo patients who received antihypertensive therapy showed no difference in deterioration or death at 24 hours, favorable outcome at 24 hours, or favorable outcome at 3 months compared with hypertensive placebo patients who did not receive antihypertensive therapy. The only significant difference detected was a lower frequency of death at 3 months for placebo patients hypertensive at admission who received antihypertensive therapy (1 of 22 [5%]) compared with those who did not (13 of 43 [30%]; P<0.05). This difference could result from chance, given the number of clinical outcomes that were compared.

The antihypertensive therapy used in the NINDS study was modest in its effects and had little potential for overshoot. Hypertensive placebo patients who received the antihypertensive therapy after randomization did not have a greater maximum decline in mean arterial pressure over the first 24 hours compared with hypertensive patients who did not receive antihypertensive therapy. In addition, abrupt declines in BP were not more pronounced among placebo patients who were treated with antihypertensive therapy compared with those who were not, reflecting the careful use and gentle effects of the antihypertensive therapy administered in this study (Appendix 2).

The interaction of antihypertensive therapy with intravenous tPA in this exploratory analysis is intriguing, but interpretations should be cautious. For the patients randomized to receive tPA, antihypertensive therapy administered before tPA was not associated with differences in early or late outcomes. However, hypertensive tPA patients who received antihypertensive therapy had a more pronounced abrupt decline in mean arterial BP. Hypertensive tPA patients who received antihypertensive therapy after randomization were less likely to have a favorable outcome at 3 months than hypertensive tPA patients who did not. One possible explanation is the nonrandomized administration of antihypertensive therapy at the bedside. Investigators could have been more likely to treat hypertensive patients they judged to be sicker. Thus, pharmacological treatment of elevated BP in these settings may be a marker rather than the cause of less favorable outcomes after tPA. This possible explanation is weakened somewhat by the fact that tPA patients treated with antihypertensive therapy did not differ significantly from tPA patients not treated with antihypertensive therapy, with respect to age, severity of stroke, or severity of hypertension. A second possible explanation is that patients for whom tPA is ineffective would be more likely to develop large infarcts, increased intracranial pressure and herniation, deterioration in neurological function, and associated elevation of arterial BP. Also, tPA patients who develop an intracerebral hemorrhage usually have marked elevations of arterial BP that require antihypertensive therapy. Even though the difference in 3-month outcome remained significant after excluding the tPA patients with symptomatic ICH who were hypertensive after randomization and after adjusting for the covariates listed, firm inference may still be inappropriate because the trial was not designed to test the effects of antihypertensive therapy. In addition, the analyses were post hoc; patient groups were small, with attendant limitations on statistical power leading to type 2I errors; and multiple comparisons were performed, leading to type 1 errors.

We cannot rule out the possibility that treatment of elevated BP after treatment with tPA may relate to a worse outcome in some stroke patients by unknown mechanisms. However, the fundamental result of the NINDS trial was that tPA patients had more favorable outcomes at 3 months than did placebo patients. Reduction in the hemorrhage rate by careful treatment of hypertension may have been responsible in part, as evidenced by the lower rate of ICH in the NINDS trial compared with other thrombolytic therapy trials.16–18 Accordingly, the NINDS investigators continue to support the management of elevated BP as specified in Appendix 2. A randomized trial would be necessary to address adequately the effects of antihypertensive therapy on BP and on clinical outcome.

In summary, hypertension was a common phenomenon in the NINDS trial. BP eligibility criteria were applied in a balanced fashion. The antihypertensive therapy was designed for, and resulted in, modest effects on BP with low potential for overshoot. The results do not suggest that use of antihypertensive therapy adversely affected BPs or clinical outcomes of placebo-randomized patients. The effects of antihypertensive therapy following treatment with tPA are complex and merit further study. Careful attention to BP and gentle management remain warranted for stroke patients treated with tPA.

Appendix 1
The following individuals and institutions participated in the NINDS rt-PA Stroke Trial.


University of Texas Medical School, Houston (104): Principal Investigator, J.C. Grotta; Coinvestigators, T. DeGraba, M. Fisher, A. Ramirez, S. Hanson, L. Morgenstein, C. Sils, W. Pasteur, F. Yatsu, K. Andrews, C. Villar-Cordova, P. Pepe; Study
Appendix 2
Guidelines for Blood Pressure Management in the NINDS rt-PA Stroke Study

(Not intended for management outside this protocol)

1. During the first 2 hours of treatment, blood pressure must be examined every 15 minutes. From 2 to 8 hours, blood pressure must be examined every 30 minutes. From 9 to 24 hours, blood pressure must be examined hourly.

2. If diastolic BP is >140 mm Hg, start an infusion of sodium nitroprusside (0.5 to 10 μg/kg/min).

3. If systolic BP is >230 mm Hg and/or diastolic BP is 121 to 140 mm Hg, labetalol 10 mg intravenously over 1 to 2 minutes is recommended. The dose may be repeated or doubled every 10 to 20 minutes, up to 150 mg.

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