Age Determines the Effects of Blood Pressure Lowering During the Acute Phase of Ischemic Stroke
The TICA Study

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Abstract—To increase understanding of the influence of blood pressure (BP) changes on functional outcome, we designed a multicenter, prospective, observational study involving patients with ischemic stroke. We included 1092 patients with ischemic stroke. BP was measured on admission and after 8, 16, 24, 32, 40, and 48 hours, and the averages of the readings were taken every 8 hours on days 3 to 7, at the day of discharge, and at 3 months. The main study variable was modified Rankin scale at 3 months. Systolic BPs >181 mm Hg at the emergency department and after 24 hours were associated with poor prognosis (odds ratio [OR]: 2.2, 95% CI: 1.2 to 4.2 and OR: 1.3, 95% CI: 1.1 to 2.3, respectively); systolic BP <136 mm Hg at the emergency department also determined worse prognosis at 3 months (OR: 1.3; 95% CI: 1.1 to 2.9). The influence of systolic BP changes in the first hours depended on patient age. In elder patients (>70 years), reductions in systolic BP determined a significant increase in the proportion of patients with worse prognosis. In patients >80 years of age, decreases in systolic BP >27.2 mm Hg determined a worse prognosis in patients with antihypertensive treatment at the emergency department (n=91) compared with those who did not receive treatment (n=106; OR: 21.7, 95% CI: 13.6 to 33.5 versus OR: 8.5, 95% CI: 3.2 to 19.6). In summary, the effect of BP modification during the acute phase of ischemic stroke on functional outcome is strongly dependent on age. (Hypertension. 2009;54:00-00.)

Key Words: ischemic stroke ▪ blood pressure ▪ age ▪ prognosis ▪ treatment

Recommendations on the management of arterial pressure in the acute phase of cerebral ischemia have not been modified in the most recent American Heart Association guidelines, and a cautious approach to the treatment of hypertension continues to be advised. Antihypertensive treatment continues to be recommended for patients with readings of ≥220/120 mm Hg, except for patients treated with thrombolytic therapy. A sudden reduction in blood pressure (BP) is undoubtedly associated with neurological worsening and is possibly associated with the reduction of perfusion pressure in ischemic cerebral areas. 

A previous study carried out in 2 university hospitals on 304 ischemic stroke patients within 24 hours of onset showed that a reduction in arterial systolic or diastolic pressure >20 mm Hg within the first 24 hours was associated with an increase in neurological deterioration, worse outcome at 3 months, and a higher infarct volume. Nevertheless, several pharmacological studies suggest that there is a benefit to a moderate decrease in arterial pressure in the acute phase of ischemic stroke. To increase understanding of the behavior and influence of BP changes, we designed a multicenter, prospective, and observational study involving patients with ischemic stroke within 24 hours of onset.

Patients and Methods
Inclusion criteria were as follows: (1) ischemic strokes before 24 hours after the onset of symptoms or from time of awakening if symptoms were already present; (2) symptoms lasting ≥1 hour and present at the time of inclusion; (3) previous independent functional situation (modified Rankin scale [mRS] <2); (4) computed tomography (CT) confirming an ischemic stroke or excluding other entities; and (5) consent given by patients or their relatives. Patients who, in the researcher’s opinion, had serious systemic disease and life expectancy of <6 months, as well as those with an intercurrent process causing hemodynamic instability, were excluded.

The study was carried out with patients admitted to hospitals and by neurologists trained in cerebrovascular disease. The patients were treated according to the recommendations of the Cerebrovascular Diseases Study Group of the Spanish Society of Neurology. Management of patients before inclusion was provided by other profes-

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The follow-up time of the study was 3 months. Demographic variables, time from onset of symptoms, vascular risk factors, and existence and type of antihypertensive treatment before stroke were included. For the determination of arterial pressure in the emergency department (ED), an average of all of the BP readings from the beginning of the clinical process to the time of admission was calculated, and any antihypertensive treatment was noted. After inclusion, 16 clinical and analytic parameters were considered: CT scan data at admission and neurological situation according to the Canadian Stroke Scale assessed at the time of admission; at 8, 16, 24, 32, 40, and 48 hours; at discharge; and after 3 months (N=1092). The study included 1092 patients from 12 hospitals (see Appendix), of which 902 were appropriate for the study of the principal variable. Thirty-six patients were not included for not satisfying any of the inclusion criteria: 19 for serious systemic disease, 11 for life expectancy of <6 months, and 8 for an intercurrent process causing hemodynamic instability. Sixty-five patients were excluded because of a lack of information and 51 for incomplete follow-up. A total of 35% of the patients presented a poor outcome at 3 months. Table 1 shows the variables that influenced the outcome on admission and within the first 24 hours.

### Results

The study included 1092 patients from 12 hospitals (see Appendix), of which 902 were appropriate for the study of the principal variable. Thirty-six patients were not included for not fulfilling any of the inclusion criteria: 19 for serious systemic disease, 11 for life expectancy of <6 months, and 8 for an intercurrent process causing hemodynamic instability. Sixty-five patients were excluded because of a lack of information and 51 for incomplete follow-up. A total of 35% of the patients presented a poor outcome at 3 months. Table 1 shows the variables that influenced the outcome on admission and within the first 24 hours.

A total of 172 patients (19.1%) received antihypertensive treatment in the ED (83 received angiotensin-converting enzyme inhibitors; 38, β-blockers; 17, diuretics; 16, calcium antagonists; and 18, sodium nitroprusside). Levels of arterial BP were higher in patients who received antihypertensive drugs (systolic BP [SBP]: 188.2 versus 153.9 mm Hg, P<0.0001; diastolic BP [DBP]: 99.8 versus 85.1 mm Hg, P<0.0001). Twelve hours after admission, 132 patients (14.6%) had received antihypertensive treatment (94 received angiotensin-converting enzyme inhibitors; 8,

### Table 1. Variables Registered on Admission and During the First 24 Hours With Influence on the Outcome at 3 Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Good Outcome (N=586)</th>
<th>Poor Outcome (N=310)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.3±10.5</td>
<td>74.3±11.2</td>
<td>&lt;0.0001</td>
<td>1.03 (1.02 to 1.05)</td>
</tr>
<tr>
<td>Female, %</td>
<td>45.6</td>
<td>49.4</td>
<td>0.153</td>
<td></td>
</tr>
<tr>
<td>Time to delay, h</td>
<td>8.5±6.4</td>
<td>7.2±5.5</td>
<td>0.002</td>
<td>0.96 (0.94 to 0.99)</td>
</tr>
<tr>
<td>Previous stroke, %</td>
<td>19.1</td>
<td>17.8</td>
<td>0.342</td>
<td></td>
</tr>
<tr>
<td>Previous hemorrhage, %</td>
<td>1.0</td>
<td>0.6</td>
<td>0.427</td>
<td></td>
</tr>
<tr>
<td>Cardiopathy, %</td>
<td>34.5</td>
<td>39.5</td>
<td>0.081</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension, %</td>
<td>61.8</td>
<td>66.1</td>
<td>0.112</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>22.6</td>
<td>25.4</td>
<td>0.191</td>
<td></td>
</tr>
<tr>
<td>Axillary temperature, °C</td>
<td>36.2±0.5</td>
<td>36.4±0.7</td>
<td>&lt;0.0001</td>
<td>1.7 (1.3 to 2.2)</td>
</tr>
<tr>
<td>Glycemia, mg/dL</td>
<td>135.7±60.4</td>
<td>140.8±54.6</td>
<td>0.243</td>
<td></td>
</tr>
<tr>
<td>Canadian Stroke Scale (range)</td>
<td>8.0 (6.0, 9.0)</td>
<td>5.0 (3.0, 6.5)</td>
<td>&lt;0.0001</td>
<td>0.6 (0.5 to 0.6)</td>
</tr>
<tr>
<td>CT: early signs of ischemia, %</td>
<td>47.3</td>
<td>67.1</td>
<td>&lt;0.0001</td>
<td>2.3 (1.7 to 3.0)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td>0.188</td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic, %</td>
<td>23.6</td>
<td>27.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiembolic, %</td>
<td>29.4</td>
<td>34.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar, %</td>
<td>26.9</td>
<td>18.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indeterminate, %</td>
<td>20.1</td>
<td>20.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive treatment at ED, %</td>
<td>11.6</td>
<td>30.7</td>
<td>&lt;0.0001</td>
<td>3.4 (2.4 to 4.8)</td>
</tr>
<tr>
<td>Highest temperature day 1, °C</td>
<td>36.4±0.5</td>
<td>36.6±0.6</td>
<td>&lt;0.0001</td>
<td>2.2 (1.6 to 2.8)</td>
</tr>
<tr>
<td>Highest glycemia day 1, mg/dL</td>
<td>126.0±49.3</td>
<td>134.4±49.4</td>
<td>0.026</td>
<td>1.41 (1.02 to 2.31)*</td>
</tr>
<tr>
<td>Antihypertensive treatment day 1</td>
<td>11.2</td>
<td>18.2</td>
<td>0.003</td>
<td>1.8 (1.2 to 2.6)</td>
</tr>
</tbody>
</table>

Quantitative variables are expressed as mean±SD or as the median (25%, 75%), unless otherwise specified. mRS =2 indicates good outcome; mRS >2, poor outcome.

*Data are expressed as the OR per 10 mg/dL.
β-blockers; 11, antagonists of the angiotensin receptors; 3,
calcium antagonists; 16, diuretics; and 46, combinations of the
previous ones). The levels of arterial BP were higher in patients
who received antihypertensive treatment (SBP: 159.1±35.6
versus 145.8±21.9 mm Hg; P<0.0001; DBP: 81.7±15.0 versus
78.1±13.3 mm Hg; P<0.0001).

The raw OR of the prognostic influence of each of the
quintiles of BP in the ED presented a U distribution, although
only levels >181 mm Hg of SBP and 100 mm Hg of DBP
attained statistical significance (OR: 2.04, 95% CI: 1.02 to
3.06 and OR: 1.16, 95% CI: 1.02 to 2.11, respectively; Figure
1). After adjustment by age, time to delay from stroke onset,
axillary temperature on ED, Canadian Stroke Scale on ad-
mission, and early signs of ischemia in CT on admission).

The evolution of SBP and DBP levels at each time interval
throughout the follow-up period for patients with and without
antihypertensive treatment is shown in Figure 2. The differences
were especially significant in the first 8 hours of evolution.

The differences between BP values measured in the ED
and after range between an increase of 40 and a decrease of
90 mm Hg for SBP and of 30 and 60 mm Hg, respectively, for
DBP. Moderate decreases in SBP (between 10.0 and
27.2 mm Hg) in the first 8 hours were associated with a better
prognosis in patients with and without antihypertensive treat-
ment (OR: 0.8, 95% CI: 0.4 to 0.9; OR: 0.7, 95% CI: 0.3 to
0.9, respectively). Nevertheless, decreases in SBP
>27.2 mm Hg in the first 8 hours of evolution worsen
prognosis (OR: 8.7; 95% CI: 4.9 to 15.4), especially in
patients with antihypertensive treatment (OR: 10.9; 95% CI:
3.3 to 51.5; after adjustment by age, time to delay from stroke
onset, temperature on admission, Canadian Stroke Scale on
admission, and early signs of ischemia in CT on admission).

Our data suggest that the influence of SBP changes in the
first hours depended on patient age. In patients aged >70
years, reductions in SBP were associated with a significant
increase in the proportion of patients with worse prognosis,
whereas the improvement associated with moderate decreases
in SBP occurred for patients <70 years of age (Table 2). In
patients >80 years of age, decreases in SBP >27.2 mm Hg
determined a worse prognosis in patients with antihyperten-
sive treatment at the ED (n=91) compared with those who
did not receive treatment (n=106; OR: 21.7, 95% CI: 13.6 to
33.5 versus OR: 8.5, 95% CI: 3.2 to 19.6).

Between admission and the first 8 hours at the hospital, 96
patients (10.7%) presented END; 76 (8.6%) in the first 24
hours and 73 (9.3%) in the first 48 hours. Age (71.1±10.6
versus 75.6±13.9 years), presence of early signs of cerebral
ischemia in the initial CT (51.2% versus 71.1%), administra-
tion of antihypertensive treatment in the ED (11.2% versus
71.1%), SBP on admission (156.7±27.2 versus 185.9±
27.7 mm Hg), DBP on admission (86.5±14.9 versus
97.1±15.6 mm Hg), difference between the SBP in the ED and
at 8 hours (4.4±20.5 versus 37.2±29.4 mm Hg), and the
difference between the DBP in the ED and at 8 hours
(6.4±14.4 versus 20.1±17.2 mm Hg) were all higher in
patients with END occurring in the first 8 hours (all with
P<0.0001). In the first logistic regression model using
continuous variables, the variables associated with the neu-
rological deterioration were only antihypertensive treatment
in the ED (OR: 9.3; 95% CI: 5.1 to 16.9) and the difference
between SBP in the ED and at 8 hours (OR: 1.03; 95% CI:
1.02 to 1.04). Only a decrease in SBP >27.2 mm Hg between
admission and the first 8 hours was associated with END
(OR: 4.9; 95% CI: 1.5 to 16.2); this association was higher in
patients who received antihypertensive treatment in the ED
(OR: 19.8; 95% CI: 9.6 to 31.2) after the model was adjusted
for age, the presence of early signs of ischemia in the CT, and

Figure 1. OR not adjusted for bad outcome at 3 months for the different quartiles of SBP and DBP at the ED.
SBP in the ED. In the group of patients who presented a >27.2-mm Hg difference in SBP between the ED and 8 hours, an association with END was found in patients >76 years of age, and the association was 2-fold in those >80 years of age (Figure 3).

### Discussion

Our research was based on a wide multicenter study of consecutive patients with unrestrictive inclusion criteria. We found that low arterial SBP and, particularly, the highest readings at the time of admission in patients with acute SBP in the ED. In the group of patients who presented a >27.2-mm Hg difference in SBP between the ED and 8 hours, an association with END was found in patients >76 years of age, and the association was 2-fold in those >80 years of age (Figure 3).

![Figure 2. Evolution of the levels of SBP (A) and DBP (B) in patients with and without antihypertensive treatment.](http://hyper.ahajournals.org/)

#### Table 2. OR (95% CI) of Poor Outcome at 3 Months Based on Modification of BP in the First 8 Hours

<table>
<thead>
<tr>
<th>SBP ED–SBP 8 h</th>
<th>Age, y</th>
<th>&lt;64 (n=191)</th>
<th>64 to 70 (n=190)</th>
<th>70 to 76 (n=170)</th>
<th>76 to 80 (n=180)</th>
<th>&gt;80 (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than −14.0 mm Hg</td>
<td>1.1 (0.7 to 1.7)</td>
<td>0.9 (0.6 to 1.3)</td>
<td>1.3 (0.6 to 2.3)</td>
<td>1.6 (0.7 to 3.5)</td>
<td>1.9 (1.1 to 4.2)</td>
<td></td>
</tr>
<tr>
<td>−14.0 to 0.0 mm Hg</td>
<td>1.1 (0.5 to 2.1)</td>
<td>1.2 (0.6 to 2.3)</td>
<td>1.2 (0.4 to 1.8)</td>
<td>1.3 (0.7 to 2.5)</td>
<td>1.2 (0.5 to 4.5)</td>
<td></td>
</tr>
<tr>
<td>0.0 to 10.0 mm Hg</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10.0 to 27.2 mm Hg</td>
<td>0.5 (0.3 to 0.8)</td>
<td>0.7 (0.4 to 0.9)</td>
<td>0.6 (0.3 to 0.9)</td>
<td>0.8 (0.5 to 1.1)</td>
<td>1.2 (0.8 to 2.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;27.2 mm Hg</td>
<td>1.1 (0.7 to 1.7)</td>
<td>1.9 (0.8 to 3.5)</td>
<td>5.5 (1.2 to 16.7)</td>
<td>9.8 (5.3 to 17.2)</td>
<td>14.9 (7.9 to 23.2)</td>
<td></td>
</tr>
</tbody>
</table>

Data were adjusted by time to delay from stroke onset, temperature on admission, Canadian Stroke Scale on admission, and early signs of ischemia in CT on admission.
ischemic stroke were associated with a worse functional outcome after 3 months. This effect was independent of other predictive factors, such as age, delay in hospitalization, temperature, stroke severity, and the presence of early signs of ischemia in the initial CT. This prognostic influence was true but less intense for the highest DBP readings and disappeared within the first 24 hours. The U-shaped relationship described in other studies was also observed in our study, although the association was more consistent for SBP than for DBP.

Although some studies have questioned the relationship between BP levels during the acute phase of stroke and outcome, the current knowledge seems to leave little doubt of the existence of a strong relation between high levels of arterial pressure, particularly systolic, and poor outcome. In our study, we did not collect data on the use of thrombolytic therapy, therefore we cannot establish any difference in the association between BP and prognosis in those treated with tissue plasminogen activator and those without tissue plasminogen activator. Levels of SBP on admission >180 mm Hg determine a worse outcome in the short and long terms. Therefore, our findings suggest that the recommendations to treat arterial hypertension in acute stroke candidates with thrombolytic therapy should be expanded to all patients with stroke, at least in the first hours of evolution.

The association between high BP and poor outcome is thought to be caused by the development of cerebral edema, greater serious hemorrhagic transformation, and early recurrence. Although our study is observational and was not designed for the physiopathologic identification of the reasons behind the poor outcome, of the 88 patients who died in the first 3 months (9.7% of the whole), 70.4% did so in the first 48 hours (43 patients in the first 24 hours and 19 patients between 24 and 48 hours after admission). The causes of death were cerebral edema (19 patients), hemorrhagic transformation (n=12), death from a cardiovascular origin (n=11), recurrence of stroke (n=7), sepsis (n=5), and other causes (n=8); 67% of the patients who later died presented with an SBP in the ED >181 mm Hg.

In acute stroke, changes in arterial BP and their influence on prognosis take place very early, whether induced by antihypertensive treatment or spontaneously. The loss of cerebral blood flow autoregulation mechanisms and the vasodilation caused by local acidosis mean that neuron survival depends on extreme variations in BP. However, this dependence disappears when the hemodynamic mechanisms related to ischemic penumbra become stable. There are currently no data to suggest that arterial hypertension should be treated any differently in acute stroke patients after the first 24 hours than in other hypertensive patients.

In acute stroke patients, sharp reductions in arterial BP determine a worse short- and long-term prognosis. In our study, absolute reductions of 27 mm Hg in SBP within the first 8 hours (15% below base values) multiplied by 9 the likelihood of adverse prognosis after 3 months and by 11 if antihypertensive treatment was received in the ED. This difference was more dependent on the intensity of the BP decrease in this quintile (38.6±12.2 versus 50.3±14.3 mm Hg; P<0.0001) than on the effect of the drug.

An observation in our study, which has not been described previously, is that age influences the prognosis of SBP reductions. In patients with SBP reductions >27 mm Hg occurring within the first 8 hours, the likelihood of a poor outcome was multiplied by 6 in patients aged 70 to 76 years, by 10 in patients 76 to 80 years, and by 45 in patients >80 years of age. Similar results were found regarding the association with the development of neurological deterioration: there was a 9-times greater likelihood in patients 76 to 80 years of age and an 18-times greater likelihood in patients >80 years of age.

The mechanisms by which age may cause worse functional outcomes related to both higher BP and more abrupt or severe lowering of BP were not the objective of this study, although it is probable that arterial stiffness and impaired autoregulation influence the mechanisms in patients. Moreover, stiffened arteries in the elderly have been proposed to be the primary cause of pseudohypertension; the possibility of inaccurate readings leads to a false diagnosis of hypertension, which would increase the negative effect of an abrupt decrease of BP.

In spite of the conservative recommendations in official guidelines, many neurologists and other physicians use antihypertensive treatments during the acute phase of cerebral ischemia, finding in many cases a beneficial effect. In our study, moderate reductions in SBP, between 10 and 27 mm Hg, were associated with a better prognosis at 3 months, irrespective of treatment; this improvement is clearer in younger patients and disappears in those >76 years of age.

In the absence of more energetic official recommendations, there may be an abuse of antihypertensive treatment in the ED, especially by physicians more prone to intervene. In our study, 18% of the patients received antihypertensive...
treatment in the ED; of these, 40% presented SBP <180 mm Hg and 13% <150 mm Hg. A total of 47% of the patients with SBP <166 mm Hg in the ED who received antihypertensive treatment presented a poor outcome at 3 months; this percentage was 9.2% in the patients with SBP >166 mm Hg who received treatment.

Perspectives
Despite the limitations of an observational study, we suggest that generalizing the current recommendations on the management of arterial BP for patients who are candidates for thrombolytic treatment to all ischemic stroke patients would lead to improved functional outcomes, both in the short and long terms. The use of antihypertensive drugs should avoid sudden decreases in BP of >10% from baseline levels, especially in elderly people.

Appendix
J.C. coordinated the study. All of clinical data in the TICA Study were collected from the following departments: Department of Neurology, Hospital Clínico Universitario, Santiago de Compostela (Rogelio Leira, 364 patients); Department of Neurology, Hospital Universitario Gregorio Marañón, Madrid (Josef Leira, 48 patients); Department of Neurology, Hospital San Juan de la Cruz, Toledo (Jose Vivancos, 24 patients); Department of Neurology, Hospital Arquitecto Marcide, Ferrol (Exuperio Díez-Tejedor, 157 patients); Department of Neurology, Hospital Clínico Universitario, Santiago de Compostela (Rogelio Leira, 364 patients); Department of Neurology, Hospital Universitario Gregorio Marañón, Madrid (Josef Leira, 48 patients); Department of Neurology, Hospital San Juan de la Cruz, Toledo (Jose Vivancos, 24 patients); Department of Neurology, Hospital University of the Princess, Madrid (Josef Egido, 16 patients); and Unit of Neurology, Hospital Arnau de Vilanova, Valencia (Ana Pareja, 6 patients).

Acknowledgments
We gratefully acknowledge the contribution of the TICA Study Group, the members of which are listed in the Appendix.

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Disclosures
None.

References
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