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

The TICA Study

Rogelio Leira, Mónica Millán, Exuperio Díez-Tejedor, Miguel Blanco, Joaquín Serena, Blanca Fuentes, Manuel Rodríguez-Yáñez, Mar Castellanos, Aida Lago, Antonio Dávalos, José Castillo, for the TICA Study, Stroke Project, Cerebrovascular Diseases Group of the Spanish Neurological Society

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;54:769-774.)

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 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;54:769-774.)

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

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 Study, Stroke Project, Cerebrovascular Diseases Group of the Spanish Neurological Society...
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.

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 inclusion in the study 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 at the time of admission; at 8, 16, 24, 32, 40, and 48 hours. Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria were used for the diagnosis of stroke. The main study variable was functional outcome determined by mRS after 3 months; we considered mRS > 2 as poor outcome. END (within the first 24 hours) was used as a secondary variable.

BP was measured on admission and after 8, 16, 24, 32, 4, and 48 hours along with the average of the readings every 8 hours on days 3, 4, 5, 6, and 7 and at the day of discharge, as well as at the 3-month follow-up (±15 days). All of the antihypertensive treatments administered during 3 months of follow-up were recorded.

The statistical analysis was performed with SPSS 16.0 for Windows (SPSS Inc.). According to the type of distribution, the quantitative variables were expressed as mean ± SD or as the median (25%, 75%), and the differences were estimated by the Student t or the Mann-Whitney-Wilcoxon test. The qualitative variables were expressed as percentages and were analyzed by means of the χ2. Quantitative variables were categorized in quintiles, because they did not satisfy the premise of linearity for logistic regression. The impact of the BP figure for every quintile and their modifications were determined by logistic regression analysis after adjusting the significant variables in the univariate analysis.

### 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 ± 28.1 versus 153.9 ± 24.8 mm Hg, ...
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 admission, and early signs of ischemia in CT on admission, systolic pressures $>$181 mm Hg at ER and after 24 hours were associated with poor prognosis (OR: 2.2, 95% CI: 1.2 to 4.2 and OR: 1.3, 95% CI: 1.1 to 2.3, respectively); systolic pressure $<$136 mm Hg at the ED also determined a worse prognosis at 3 months (OR: 1.3; 95% CI: 1.1 to 2.9). The influence of diastolic pressure was less significant. Levels of BP measured 24 hours after admission did not significantly influence outcome (data not shown).

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 treatment (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). Modifications in DBP in this period of time were not significant.

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 antihypertensive 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%), administration 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 neurological 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 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).

<table>
<thead>
<tr>
<th>SBP ED−SBP 8 h</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 2.4)</td>
<td>1.6 (0.7 to 3.1)</td>
<td>1.9 (1.1 to 4.2)</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 2.5)</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>
</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>
</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>
</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>
</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.
Although some studies have questioned the relation between BP levels during the acute phase of stroke and outcome,9–12 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.4,8,13–18 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.1 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.3 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 hypertension patients.

In acute stroke patients, sharp reductions in arterial BP determine a worse short- and long-term prognosis.5,4,19 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 15 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.30 Moreover, stiffened arteries in the elderly have been proposed to be the primary cause of pseudohypertension21,22; 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,16,23–26 finding in many cases a beneficial effect.5,16,17,22 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.\(^{25}\) 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 Doctor Josep Trueta, Gerona (Antonio Dávalos, 208 patients); Department of Neurology, Hospital Universitario de la Paz, Madrid (Exupero Díez-Tejedor, 157 patients); Department of Neurology, Hospital Universitario de la Fe, Valencia (Aída Lago, 83 patients); Unit of Neurology, Hospital Arquitecto Marcide, Ferrol (Javier López, 79 patients); Department of Neurosciences, Hospital Universitario Germans Trias i Pujol, Badalona (Mónica Millán, 54 patients); Department of Neurology, Hospital Virgen Blanca, León (Javier Tejada, 48 patients); Department of Neurology, Hospital San Pedro de Alcántara, Cáceres (José Ramírez, 28 patients); Department of Neurology, Hospital Universitario Gregorio Marañón, Madrid (Antonio Gil, 25 patients); Department of Neurology, Hospital Universitario de la Princesa, Madrid (José Vivancos, 24 patients); Department of Neurology, Hospital Clínico San Carlos, Madrid (José Egoz, 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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