Send Orders for Reprints to reprints@benthamscience.net

10 *The Open Hypertension Journal,* **2014**, *6,* 10-11

Open Access

CONGRESS COVERAGE

Antihypertensive Therapy in Acute Ischemic Stroke: Lost in the Mist

Konstantinos Tziomalos[1], Vasilios G. Athyros[2] and Michael Doumas[2,3,*]

[1]*First Prop. Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece;* [2]*Second Prop. Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki, Greece;* [3]*Veteran Administration Medical Center and George Washington University, Washington, DC, USA*

Keywords: Acute stroke, ischemic, hypertension, antihypertensive drugs.

The results of the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) study were presented last month at the 2013 American Heart Association Scientific Meeting and simultaneously published in the Journal of the American Medical Association [1]. The CATIS study was a multicenter, controlled, randomized study that aimed to assess the effects of blood pressure reduction during the acute phase of ischemic stroke on death and major disability at 14 days and 3 months after the episode. The stroke was confirmed by brain CT or MRI and systolic blood pressure levels between 140-220 mmHg were required to enter the study. About half of screened patients with an acute ischemic stroke and hypertension fulfilled all inclusion/exclusion criteria and entered the study (2,038 out of 4,071).

Study participants were randomly assigned to receive or not antihypertensive therapy within 48 hours of stroke onset. In particular, a graded blood pressure reduction was aimed in the active group targeting a 10-25% reduction during the first study day and blood pressure control during the first week post-randomization. In contrast, no antihypertensive therapy was given in the control group and previous antihypertensive medication was discontinued during the acute phase of stroke. After the first week, all patients received antihypertensive therapy to achieve blood pressure control (<140/90 mmHg).

Blood pressure was significantly reduced in both groups during the first 24h post-randomization; however, the reduction was significantly greater in the active compared to the control group (21.8 versus 12.7 mmHg; between group difference: 9.1 mmHg; 95% CI: 8.1-10.2; p<0.001). Similarly, blood pressure levels were significantly lower in the active group at 7 days post-randomization (between group difference 9.3 mmHg; 95% CI: 8.4-10.1; p<0.001). The primary outcome (death or major disability at 14 days or hospital discharge) was identical in the two groups (odds ratio: 1.00; 95% CI: 0.88-1.14; p=0.98). The secondary outcome (death or major disability at 3 months post-randomization) was also the same (odds ratio: 0.99; 95% CI: 0.86-1.15; p=0.93), despite lower blood pressure values in the active group.

Subgroup analysis did not reveal any significant differences between the two groups on study outcomes. Blood pressure reduction during the acute phase of stroke seemed to confer a significant benefit only in one subgroup of patients: those who received antihypertensive therapy after the first 24h of stroke onset (odds ratio: 0.73; 95% CI: 0.55-0.97; p=0.03). It has to be noted however that the findings of the subgroup analysis should always interpreted with caution, and be considered rather as hypothesis generating than conclusive.

The results of the CATIS study add more gas on the debate about the management of elevated blood pressure during the acute phase of an ischemic stroke. Current guidelines recommend blood pressure lowering in acute ischemic stroke only when blood pressure levels are above 220/120 mmHg [2]. However, such patients represent a minority, with less of 1% of patients admitted for stroke [3]. Therefore, a therapeutic strategy for the vast majority of stroke patients with elevated blood pressure is of utmost importance for practicing clinicians.

Available data in this field is unfortunately limited and inconclusive. About a decade ago, the Acute Candesartan Cilexitil Therapy in Stroke Survivors (ACCESS) study created a lot of enthusiasm [4]. A significantly lower rate of vascular events and all-cause mortality at 12 months was observed with candesartan compared to placebo (odds ratio: 0.475; 95% CI: 0.252-0.895), and the study was prematurely terminated when almost 350 patients were randomized instead of the projected 500 patients.

The ACCESS study questioned the negative findings of the Intravenous Nimodipine West European Stroke Trial (INWEST) [5], and set the basis for the conduction of a larger study, the Scandinavian Candesartan Acute Stroke Trial (SCAST). In the latter study, candesartan was compared to placebo in more than 2,000 patients with acute stroke, either ischemic or hemorrhagic [6]. Unfortunately, the great expectations generated by the ACCESS study were

*Address correspondence to this author at the Veteran Administration Medical Center and George Washington University, Washington, DC, USA; Tel: +30 2310992836; Fax: +30 2310 835955;
E-mail: michalisdoumas@yahoo.co.uk

1876-5262/14 2014 Bentham Open

not fulfilled. There was no significant difference in the outcome between the active and the placebo group of the trial.

In the meantime, two other smaller studies were published. The Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS), a placebo-controlled, randomized study of 179 patients with acute stroke compared the effects of labetalol, lisinopril, and placebo [7]. No significant differences between the active and the comparison groups were observed, apart from a marginal benefit in mortality at 3 months post-stroke (hazard ratio: 0.40; 95% CI: 0.2-1.0; p=0.05). The Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS) compared the effects of continuation or withdrawal of prior antihypertensive therapy in 763 patients with an acute mild stroke [8]. Continuation of antihypertensive therapy did not confer any benefit in mortality or disability.

Taken together, the findings of the CATIS trial combined with the findings of previous trials point towards a neutral effect of antihypertensive therapy during the acute phase of an ischemic stroke. Whether the time of therapy initiation (>24h from stroke onset) or other yet unidentified factors play a role and might identify patient subgroups who will benefit from antihypertensive therapy remains to be clarified by future research. Until then, the 'non-detrimental – non-beneficial' effect of antihypertensive therapy suggests the individualization of management during the acute stroke by treating physicians.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENT

Declared none.

REFERENCES

[1] He J, Zhang Y, Xu T, *et al*. for the CATIS Investigators. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke. JAMA 2013; 311(6): 575-6.

[2] Jauch EC, Saver JL, Adams HP Jr, *et al*. American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44: 870-947.

[3] Qureshi AI, Ezzeddine MA, Nasar A, *et al.* Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. Am J Emerg Med 2007; 25: 32-38.

[4] Schrader J, Luders S, Kulschewski A, *et al.* The ACCESS study: evaluation of acute candesartan cilexitil therapy in stroke survivors. Stroke 2003; 34: 1699-703.

[5] Wahlgren NG, MacMahon DG, DeKeyser J, Indrdavik B, Ryman T. Intravenous Nimodipine West European Stroke Trial (INWEST) of nimodipine in the treatment of acute ischaemic stroke. Cerebrovasc Dis 1994; 4: 204-10.

[6] Sandset EC, Bath PM, Boysen G, *et al*. SCAST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet 2011; 377: 741-50.

[7] Potter JF, Robinson TG, Ford GA, *et al.* Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. Lancet Neurol 2009; 8: 48-56.

[8] Robinson TG, Potter JF, Ford GA, *et al*. COSSACS Investigators. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. Lancet Neurol 2010; 9: 767-75.

Received: January 20, 2014 Revised: January 24, 2014 Accepted: February 02, 2014

© Tziomalos *et al.*; Licensee *Bentham Open.*

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/-licenses/by-nc/3.0/) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.