ORIGINAL ARTICLE

Blood Pressure as an Independent Prognostic Factor in Acute Ischemic Stroke

Matt B. Jensen, Bongin Yoo, William R. Clarke, Patricia H. Davis, Harold P. Adams, Jr.

ABSTRACT: ***Background and Purpose:*** Blood pressure is elevated in most patients during acute ischemic stroke, but the prognostic significance of this is unclear as the current data yield conflicting results. ***Methods:*** Admission blood pressure from the 1281 patients in the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) was analyzed for prognostic significance as well as the risk of hemorrhagic transformation. We also examined weighted-average blood pressure over seven days, and the impact of a 30% change in blood pressure in 24 hours. Patients with severe hypertension were excluded from the TOAST trial. ***Results:*** Increasing systolic blood pressure (SBP) on admission, but not diastolic (DBP) or mean arterial pressure (MAP) was predictive of poor outcome, but this effect was not significant after adjustment for other know prognostic factors. Increasing weighted-average SBP and MAP over seven days were predictive for poor outcome, but a 30% change in blood pressure over 24 hours was not. ***Conclusions:*** Admission blood pressure is not an independent prognostic factor in acute ischemic stroke, but the weighted-average of SBP and MAP over seven days probably does have predictive value with higher values having a worse prognosis. A prospective trial of blood pressure control during acute stroke is needed.

RÉSUMÉ: La tension artérielle comme facteur indépendant prédisant l'accident vasculaire cérébral aigu. ***Contexte et objectif:*** La tension artérielle est élevée chez la plupart des patients pendant un accident vasculaire cérébral aigu. Cependant, les données disponibles à ce sujet sont discordantes et sa valeur pronostique demeure incertaine. ***Méthodes:*** Nous avons analysé les données de tension artérielle de 1 281 patients participant au Trial of ORG 10172 in Acute Stroke Treatment (TOAST) pour en déterminer la signification pronostique ainsi que le risque de transformation hémorragique. Nous avons également examiné la tension artérielle moyenne pondérée sur une période de sept jours et l'impact d'un changement de la tension artérielle de 30% en 24 heures. Les patients porteurs d'une hypertension sévère étaient exclus de l'étude TOAST. ***Résultats:*** Une tension artérielle systolique (TAS) à la hausse au moment de l'admission prédisait une issue défavorable, ce qui n'était pas le cas de la tension artérielle diastolique (TAD) ou de la tension artérielle moyenne (TAM). Cet effet n'était pas significatif après ajustement pour d'autres facteurs pronostiques connus. Une moyenne pondérée de la TAS et de la TAM qui augmente sur une période de sept jours prédisait une issue défavorable, ce qui n'était pas le cas pour un changement de 30% dans la TA en 24 heures. ***Conclusions:*** La TA à l'admission n'est pas un facteur pronostique indépendant de l'accident vasculaire cérébral aigu, mais la moyenne pondérée de la TAS et de la TAM sur une période de sept jours comporte probablement une valeur prédictive, les valeurs les plus hautes ayant le pronostic le moins bon. Le contrôle de la tension artérielle pendant l'accident vasculaire cérébral aigu devra faire l'objet d'une étude prospective.

Can. J. Neurol. Sci. 2006; 33: 34-38

Hypertension increases the risk for first and recurrent stroke[1] and lowering of the blood pressure is effective for both primary and secondary prevention of stroke.[2-5] Most patients with acute ischemic and hemorrhagic stroke have elevations in blood pressure that spontaneously resolve over the first week.[6-8] Some studies show that either a high or low blood pressure at the time of admission is an independent prognostic factor for poor outcome after stroke.[9-13] However, other studies show no such relationship, especially after adjustment for other known

From the Stroke Center, University of California, San Diego (MBJ), San Diego, California; Department of Neurology, University of Iowa College of Medicine (PHD, HPA) and Department of Biostatistics (BY, WRC), University of Iowa College of Public Health, Iowa City, Iowa, USA

RECEIVED MAY 25, 2005. ACCEPTED IN FINAL FORM AUGUST 13, 2005.

Reprint requests to: Matt B. Jensen, Stroke Center, University of California, San Diego, OPC 3rd Floor Suite 3, 200 W. Arbor Dr., San Diego, CA 92103-8466, USA

prognostic factors.[14-19] Because the prognostic influence of initial blood pressure on outcome has not been established, we analyzed data from the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) study.[20] We also evaluated the interaction between initial blood pressure and the risk of hemorrhagic transformation. In addition, we investigated the potential effect of weighted-average blood pressure during the first week, or the changes in blood pressure from admission to 24 hours as a predictor of outcome.

Methods

There were 1281 patients with acute ischemic stroke enrolled in the TOAST study, which was a randomized, double-blind, placebo-controlled, multicenter trial of a heparinoid started within 24 hours of acute ischemic stroke and continued for seven days. Inclusion criteria were age 18 to 85 years, onset of ischemic stroke between one and 24 hours, and estimated prestroke modified Barthel Index of 12 or more. Patients were excluded if symptoms resolved or were mild, in a coma, had mass effect, blood, or nonvascular cause for symptoms on scan, active bleeding, surgery within 24 hours, a medical need or contraindication to anticoagulation, abnormal coagulation studies, severe or terminal medical illness. Another exclusion criteria that impacted this analysis was exclusion for mean arterial pressure (MAP) of greater than 130 mm Hg. Treatment of blood pressure during the study was left at the discretion of the treating physician; these data were not recorded and unavailable for this analysis. The outcome measures were assessed at seven and 90 days after stroke, the 90 day values were used for this analysis. The modified Barthel Index is a disability scale for stroke patients, the items can be divided into a group that is related to self-care (feeding, grooming, bathing, dressing, bowel and bladder care, and toilet use) and a group related to mobility (ambulation, transfers, and stair climbing). The Glasgow Outcome Scale and the modified Barthel Index were chosen as the trial endpoints because they were validated instruments to assess disability at that time; the Rankin scale and the National Institutes of Health Stroke Scale (NIHSS) could also have been used but were not as well established then as they are now. Hemorrhagic transformation of the infarct was assessed by the treating physician and a blinded central neuroradiologist on a HCT performed on day seven or earlier if it was clinically indicated; there was no grading of the hemorrhage, and there were more intracerebral hemorrhages in the group assigned to the heparinoid. A single systolic (SBP) and diastolic blood pressure (DBP) were recorded at admission to the hospital (all patients were less than 24 hours from symptom onset), from which we were able to calculate MAP, then a single blood pressure was taken daily for seven days, and outcome data were available for all patients. For this trial, patients were excluded if they had a MAP > 130 mm Hg.

Good outcome was defined as a combined Glasgow Outcome Scale of I or II and a modified Barthel Index of 12 or greater, with poor outcome defined as anything less than this including death. In statistical analysis, we evaluated outcome as well as the incidence of hemorrhagic transformation as dependent variables. The independent variables were SBP, DBP, MAP, age, race, gender, NIHSS score, blood glucose level on admission, history of hypertension, history of diabetes, adjudicated stroke subtype, and treatment group. These potential confounders were picked by clinical common sense and not the product of an analysis; the NIHSS was used specifically to adjust for the confounding effect of the association between stroke severity and hypertension. The blood pressures were analyzed as continuous variables and grouped in quartiles. The three higher quartiles of blood pressure were compared to the lowest. We also analyzed the data based on the time blood pressure was taken from symptom onset (all patients presented within 24 hours for the trial).

The SBP, DBP, and MAP were also evaluated as a weighted-average over seven days (calculated by the area under the curve of recorded BP divided by the measurement period of seven days) for outcome, as well as evaluating the change in SBP, DBP, and MAP from admission and 24 hours to see if an increase or decrease of 30% would predict outcome.

A logistic regression model was used to examine each blood pressure group first in univariate analysis, then with the other independent variables in multivariable analysis. Results are shown as the odds ratio (OR) with 95% confidence intervals (95% CI), with significance defined as $p<0.05$. No adjustments were made for multiple comparisons.

Table 1: Univariate and multivariable odds ratios for a good stroke outcome with initial blood pressure measured as a continuous variable

BP	Univariate	95% CI	P value	Multivariable	95% CI	P Value
Measure	OR*			OR†		
SBP	**0.92**	**0.87-0.97**	**0.003**	0.99	0.92-1.07	0.82
DBP	0.98	0.90-1.08	0.73	0.95	0.84-1.06	0.34
MAP	0.93	0.85-1.01	0.08	0.96	0.86-1.07	0.47

†Odds ratio of a good outcome per 10 mm Hg increase in blood pressure. Odds ratio of a good outcome adjusted for known prognostic factors (age, race, gender, NIHSS score, blood glucose level on admission, history of hypertension, history of diabetes, adjudicated stroke subtype, and treatment group) per 10 mm Hg increase in BP.

https://doi.org/10.1017/S0317167100004662 Published online by Cambridge University Press

Table 2: Multivariable odds ratios for a good stroke outcome according to blood pressure as a continuous variable and time after onset of stroke

Time of arrival	OR*	95% CI	P value
SBP 0-6 hr	0.99	0.95-1.04	0.67
SBP 7-12 hr	1.00	0.99-1.02	0.72
SBP 13-18 hr	1.00	0.99-1.02	0.77
SBP 19-24 hr	0.99	0.98-1.01	0.28
DBP 0-6 hr	0.97	0.92-1.03	0.28
DBP 7-12 hr	1.02	1.00-1.05	0.10
DBP 13-18 hr	1.00	0.98-1.02	0.94
DBP 19-24 hr	**0.98**	**0.96-0.997**	**0.03**
MAP 0-6 hr	0.98	0.92-1.03	0.37
MAP 7-12 hr	1.01	0.99-1.04	0.23
MAP 13-18 hr	1.00	0.98-1.02	0.91
MAP 19-24 hr	0.98	0.96-1.00	0.05

* Odds ratio for a good outcome per 10 mm Hg increase in pressure. Odds ratio of a good outcome adjusted for known prognostic factors (age, race, gender, NIHSS score, blood glucose level on admission, history of hypertension, history of diabetes, adjudicated stroke subtype, and treatment group) per 10 mm Hg increase in BP.

Results

The average blood pressures (standard deviation) for this trial were SBP 154 (21) mm Hg, DBP 85 (12) mm Hg, and MAP 108 (15) mm Hg. The SBP quartile breakpoints were 141, 155, and 170 mm Hg; for DBP they were 79, 87, and 92 mm Hg; for MAP they were 101, 110, and 117 mm Hg. Higher initial SBP significantly predicted reduced odds of a good outcome at three months, with every 10 mm Hg increase in SBP reducing the odds of a good outcome by 8%; DBP and MAP did not predict outcome as continuous variables (Table 1). After adjustment for other prognostic factors (age, race, gender, NIHSS score, admission blood glucose, history of hypertension, history of diabetes, stroke subtype, and treatment group), none of the blood pressure groups predicted outcome (Table 1). The SBP, DBP, and MAP as quartiles did not predict outcome in multivariable analysis.

Dividing the patients into four groups based on time of arrival and admission blood pressure recording after symptom onset; 0-6 hours (6%), 7-12 hours (26%), 13-18 hours (29%), and 19-24 hours (39%), the admission DBP in the group that presented 19-24 hours after symptom onset significantly predicted outcome even after multivariable analysis, with every ten mm Hg increase in DBP reducing the odds of a good outcome by 2%. The SBP and MAP did not predict outcome in any of the different time of arrival groups, although the MAP at 19-24 hours was borderline (Table 2).

Weighted average SBP and MAP over seven days (but not DBP) significantly predicted outcome in univariate and multivariable analysis (Table 3), where the odds of a good outcome was reduced 11% and 16% for every ten mmHg increase in the weighted average SBP and MAP, respectively.

An increase or decrease of either SBP, DBP, or MAP of 30% between admission and 24 hours was not a significant predictor of outcome. None of the baseline blood pressure parameters predicted hemorrhagic transformation as a continuous variable or in quartiles.

The weighted average BP did not predict hemorrhagic transformation as a continuous variable. The two highest quartiles of SBP and MAP (but not DBP) significantly predicted hemorrhagic transformation compared to the lowest, with a 43% higher odds of hemorrhage for SBP >158 compared to <134, and MAP >109 compared to <95 (Table 4).

Discussion

This is a post-hoc exploratory analysis of the data collected in TOAST, which tested the utility of early administration of anticoagulants in treatment of patients with recent stroke. We recognize the limitations inherent in a post-hoc study when blood pressure management was not the primary focus of this project. For example, the trial was severely limited by the exclusion of patients with markedly elevated blood pressures, which was done for the potential risk for hemorrhage secondary to the anticoagulants. In addition, while the trial included broad guidelines for blood pressure management, it did not provide specific recommendations about the use of medications, our data set did not allow for the analysis of the impact of blood pressure lowering medications. Because so many comparisons were made, it is possible that significant results are due to chance alone. We could have missed an effect of low BP as our lowest quartile was < 141. On the other hand, TOAST was a carefully conducted multi-center trial that prospectively collected data including blood pressure measurements. Patients with a broad spectrum of neurological impairments from strokes of a variety of causes were enrolled within 24 hours of onset of the vascular event. Patients were assessed closely during the first week after stroke and again at three months. Both neurological and medical events were captured. Investigators and coordinators participated in a rigorous educational and certification program in using

Table 3: Multivariable odds ratio of a good stroke outcome for weighted average blood pressure over the first week

BP increase	OR*	95% CI	P
SBP	**0.89**	**0.81-0.98**	**0.01**
DBP	0.87	0.73-1.04	0.11
MAP	**0.84**	**0.72-0.98**	**0.03**

* Odds ratio for a good Outcome per 10 mm Hg increase in blood pressure. Odds ratio of a good outcome adjusted for known prognostic factors (age, race, gender, NIHSS score, blood glucose level on admission, history of hypertension, history of diabetes, adjudicated stroke subtype, and treatment group) per 10 mm Hg increase in BP.

https://doi.org/10.1017/S0317167100004662 Published online by Cambridge University Press

Table 4: Multivariable odds ratio of absence of hemorrhagic transformation according to weighted average blood pressure over the first week (compared to lowest quartile*)

Quartiles	OR	95% CI	P value
SBP 134-146	1.09	0.67-1.77	0.72
SBP 147-158	**0.60**	**0.37-0.96**	**0.03**
SBP >158	**0.57**	**0.35-0.92**	**0.02**
DBP 73-80	1.11	0.72-1.72	0.63
DBP 81-86	0.77	0.50-1.18	0.24
DBP >86	0.80	0.50-1.26	0.33
MAP 95-102	0.88	0.55-1.39	0.58
MAP 103-109	**0.58**	**0.36-0.91**	**0.02**
MAP >109	**0.57**	**0.36-0.92**	**0.02**

* Lowest Quartile included SBP < 134 mm Hg, DBP < 73 mm Hg, MAP < 95 mm Hg. Odds ratio of a good outcome adjusted for known prognostic factors (age, race, gender, NIHSS score, blood glucose level on admission, history of hypertension, history of diabetes, adjudicated stroke subtype, and treatment group) per 10 mm Hg increase in BP.

clinical rating instruments. Extensive quality assurance programs, including comparisons of case report forms with source documents, mean that the data have a high degree of reliability.

Our study shows that the baseline blood pressure (SBP, DBP, or MAP) does not independently predict either the outcome following ischemic stroke or the risk of symptomatic hemorrhagic transformation of the infarction. Rather than being an independent predictor of unfavorable outcomes or major complications, the extremes of the presenting blood pressure appear to be a marker of other factors, such as size or severity of stroke or serious pre-morbid hypertension, which have a negative impact on patients.

We did find that elevated weighted-average SBP or MAP during seven days following stroke did predict outcomes and hemorrhagic transformation. This information should be viewed with caution for the reasons cited above. Those patients who are seriously ill, who have neurological worsening, or who have secondary hemorrhages likely will have elevated blood pressures. In these circumstances, it is not clear whether the elevated blood pressures are a cause of the poor outcomes or are indirectly related to other factors. In addition, because management of arterial blood pressure was at the discretion of the treating physicians, any correlations between the blood pressure values and outcomes must be considered as tenuous.

Our results should be evaluated in light of other publications. Many of the studies have been small and observational. Some have been retrospective and have not included specific intervals for measurement of blood pressure. A post-hoc analysis of the International Stroke Trial reported a significant J-shaped relationship between high or low SBP and poor outcome.[12] The DBP and therefore MAP were not available. While the International Stroke Trial did enroll large numbers of patients that might explain the significance of the data, the trial does have important limitations. The trial enrolled patients up to 48 hours after stroke and did not have the strenuous quality control efforts included in TOAST. Other studies provide conflicting information. The Intravenous Nimodipine West-European Stroke Trial (INWEST) trial, which tested nimodipine, was halted prematurely because of an association of poorer outcomes among actively treated patients.[21] The worsening was attributed to a decline in blood pressure. The relationship between blood pressure decline and poor outcome was attributed to the medication. In this situation, the drop in blood pressure was a secondary phenomenon. The results of the systemic review performed by Willmot et al[22] are largely driven by the results of the International Stroke Trial. While they found high blood pressure was associated with death, dependency, or deterioration, the findings were not adjusted for other known prognostic variables. In addition, the limitations of the data in the International Stroke Trial greatly influence the systematic review. The limitations of the other studies mean that their results do not either substantiate or refute our findings. Additional studies are needed to determine the true prognostic impact of baseline blood pressure readings on outcomes after stroke. At present, the data suggest that SBP, DBP, and MAP are not strong predictors of outcome. Rather than being independent forecasters, the blood pressure values reflect the overall serious nature of the illness including the severity of neurological impairments.

Additional information about the impact of the baseline blood pressure is needed because arterial hypertension is found commonly among persons with acute ischemic stroke and the proper management of the elevated blood pressure has been the source of considerable concern to physicians. The potential for a markedly elevated blood pressure to promote hemorrhagic transformation or cerebral edema has prompted some physicians to prescribe potent antihypertensive agents. A SBP > 185 mm Hg or DBP > 110 mm Hg is a contraindication for urgent intravenous thrombolysis. In addition, concomitant medical conditions such as acute myocardial ischemia, dissection of the aorta, or renal failure might necessitate rapid lowering of the blood pressure. On the other hand, a precipitous and dramatic decline in blood pressure may aggravate the ischemic process by reducing cerebral perfusion pressure. In addition, some physicians have used vasopressors to increase cerebral perfusion pressure in the setting of stroke.[23,24] Because of the uncertainty about the significance of arterial hypertension following stroke, current guidelines have provided very broad criteria for management of an elevated blood pressure.[25] The recommendations are based on no solid data, and there is evidence that they are not routinely followed.[26] Other than the nimodipine trial, the only other randomized, controlled trial of a blood pressure medication during acute ischemic stroke was the ACCESS study,[27] where candesartan was superior to placebo, however this result does not settle the issue we are addressing here as there was no difference in blood pressure between the treatment and placebo groups. As previously called for,[28,29] prospective clinical trials focusing on the proper management of arterial hypertension after stroke are sorely needed.

https://doi.org/10.1017/S0317167100004662 Published online by Cambridge University Press

References

1. Rodgers A, MacMahon S, Gamble G, Slattery J, Sandercock P, Warlow C. Blood pressure and the risk of stroke in patients with cerebrovascular disease. BMJ. 1996;313:147.
2. PATS Collaborating Group. Post-stroke antihypertensive treatment study: a preliminary result. Chin Med J. 1995;108:710-7.
3. The Heart Outcome Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342:145-53.
4. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358:1033-41.
5. LIFE study group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet. 2002;359:995-1003.
6. Jorgensen HS, Nakayama H, Christensen HR, Raaschou HO, Kampmann JP, Olsen TS. Blood pressure in acute stroke. Cerebrovasc Dis. 2002;13:204-9.
7. Britton M, Carlsson A, de Faire U. Blood pressure course in patients with acute stroke and matched controls. Stroke. 1986;17:861-4.
8. Semplicini A, Maresca A, Boscolo G, Sartori M, Rocchi R, Giantin V, et al. Hypertension in acute ischemic stroke: a compensatory mechanism or an additional damaging factor? Arch Intern Med. 2003;163:211-6.
9. Bhalla A, Wolfe CDA, Rudd AG. The effect of 24 h blood pressure levels on early neurological recovery after stroke. J Int Med. 2001;250:121-30.
10. Ahmed N, Wahlgren N. High initial blood pressure after acute stroke is associated with poor functional outcome. J Int Med. 2001;249:467-73.
11. Christensen H, Meden P, Overgaard K, Boysen G. The course of blood pressure in acute stroke is related to the severity of the neurological deficits. Acta Neurol Scand. 2002;106:142-7.
12. Leonardi-Bee J, Bath PMW, Phillips SJ, Sandercock PAG, for the IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. Stroke. 2002;33:1315-20.
13. Castillo J, Leira R, Garcia MM, Serena J, Blanco M, Davalos A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke. 2004;35:520-7.
14. Carlberg B, Asplund K, Hagg E. The prognostic value of admission blood pressure in patients with acute stroke. Stroke. 1993;24:1372-5.
15. Robinson T, Waddington A, Ward-Close S, Taub N, Potter J. The predictive role of 24-hour compared to casual blood pressure levels on outcome following acute stroke. Cerebrovasc Dis. 1997;7:264-72.
16. Chamorro A, Vila N, Ascaso C, Elices E, Schonewille W, Blanc R. Blood pressure and functional recovery in acute ischemic stroke. Stroke. 1998;29:1850-3.
17. Boreas AMHP, Lodder J, Kessels F, de Leeuw PW, Troost J. Prognostic value of blood pressure in acute stroke. J Hum Hypertens. 2002;16:111-6.
18. Aslanyan S, Fazekas F, Weir CJ, Horner S, Lees KR, for the GAIN International Steering Committee and Investigators. Effect of blood pressure during the acute period of ischemic stroke on stroke outcome: a tertiary analysis of the GAIN international trial. Stroke. 2003;34:2420-5.
19. Vlcek M, Schillinger M, Lang W, Lalouschek W, Bur A, Hirschl MM. Association between course of blood pressure within the first 24 hours and functional recovery after acute ischemic stroke. Ann Emerg Med. 2003;42:619-26.
20. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparanoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. JAMA. 1998;279:1265-72.
21. Wahlgren NG, Macmahon DG, Dekeyser J, Indredavik B, Ryman T. (INWEST) of nimodipine in the treatment of acute ischemic stroke. Cerebrovasc Dis. 1994;4:204-10.
22. Willmot M, Leonardi-Bee J, Bath PMW. High blood pressure in acute stroke and subsequent outcome: a systematic review. Hypertension. 2004;43:18-24.
23. Rordorf G, Koroshetz WJ, Ezzeddine MA, Segal AZ, Buonanno FS. A pilot study of drug-induced hypertension for treatment of acute stroke. Neurology. 2001;56:1210-3.
24. Hillis AE, Ulatowski JA, Barker PB, Torbey M, Ziai W, Beauchamp NJ, et al. A pilot randomized trial of induced blood pressure elevation: effects on function and focal perfusion in acute and subacute stroke. Cerebrovasc Dis. 2003;16:236-46.
25. Adams HP, Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, et al. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke council of the American Stroke Association. Stroke. 2003;34:1056-83.
26. Kanji S, Corman C, Douen AG. Blood pressure management in acute stroke: comparison of current guidelines with prescribing patterns. Can J Neurol Sci. 2002;29(2):125-31.
27. Schrader J, Luders S, Kulchewski A, et al. The ACCESS Study: Evaluation of acute candesartan cilexetil therapy in stroke survivors. Stroke. 2003;34:1699-703.
28. Spence JD. Hypertension and stroke. Can J Neurol Sci. 2002 May;29(2):113-4.
29. Bath P, Boysen G, Donnan G, et al. Hypertension in acute stroke: what to do? Stroke. 2001;32(7):1697-8.