Blood Pressure Management in Acute Stroke: A Long-Standing Debate

Konstantinos Spengos^a Georgios Tsivgoulis^a Nikolaos Zakopoulos^b

^aDepartment of Neurology, University of Athens School of Medicine, Eginition Hospital, and

^bDepartment of Clinical Therapeutics, University of Athens School of Medicine, Alexandra Hospital, Athens, Greece

Key Words

Acute stroke · Blood pressure · Hypertension

Abstract

Although elevated blood pressure (BP) levels are a common complication of acute stroke, whether of ischaemic or haemorrhagic type, a long-standing debate exists regarding the management of post-stroke hypertension. In the absence of solid, randomised data from controlled trials, the current observational evidence allows different approaches, since theoretical arguments exist for both lowering BP in the setting of acute stroke (reduce the risk of stroke recurrence, of subsequent oedema formation, of rebleeding and haematoma expansion in patients with cerebral bleeding) as well as leaving raised BP levels untreated (avoid reduction in cerebral perfusion pressure and blood flow to viable ischaemic tissue in the absence of normal autoregulation). The present review will summarize the evidence for and against the therapeutic manipulation of BP in acute stroke provided by the currently available observational studies and randomised trials, consider the ongoing clinical trials in this area and address the present recommendations regarding this conflicting issue.

Copyright © 2006 S. Karger AG, Basel

Introduction

Elevated blood pressure (BP) as defined by the World Health Organization and the International Society of Hypertension (systolic BP >140 mm Hg and/or diastolic BP >90 mm Hg) is established as the most prevalent modifiable risk factor for stroke. Large-scale observational studies have demonstrated that BP values are positively and continuously associated with the risk of stroke in a log-linear fashion [1]. Significant advances in primary and secondary stroke prevention using various antihypertensive agents have been achieved recently. There is now clear evidence that BP reduction protects against first-ever, as well as recurrent stroke independent of baseline BP levels [2–4]. More specifically, systemic reviews of 17 primary prevention trials involving a total of 47,000 participants showed that lowering systolic BP (SBP) by 10–12 mm Hg and diastolic BP (DBP) by 5–6 mm Hg leads to a 38% reduction in the risk of stroke [2]. Furthermore, a recent meta-analysis of 7 secondary prevention trials involving 15,527 participants demonstrated that the use of BP-lowering agents reduced the risk of recurrent stroke by 24% [4].

Elevated BP values (>140/90 mm Hg) are present in up to 80% of patients with acute stroke [5, 6], while almost every fourth patient presents with markedly raised SBP values >180 mm Hg. There is no single explanation for the

elevation of BP in acute stroke. The main contributing factors include pre-existing hypertension [7], activation of neuro-endocrine systems [8, 9], the stress of hospitalisation [10], infarct topography [11], stroke subtype [7, 12, 13], stroke severity [14] and the reactive increases in systemic BP in response to raised intracranial pressure [15].

Despite its high prevalence, the optimal management of arterial hypertension during the acute stroke stage has not been established and remains an issue of long-lasting debate and little consensus [15, 16]. Notably, the results of numerous observational studies, which investigated the relationship of admission BP levels with stroke outcome in patients with ischaemic stroke (IS; table 1) and intracerebral haemorrhage (ICH; table 2) are conflicting and data from randomised controlled studies are still missing [17, 18]. Aim of this review was not to answer this still open question, but to present a critical overview of all arguments pro and contra lowering BP in the acute setting of stroke on the basis of current observational and randomised evidence, consider the ongoing clinical trials in this area and address the present recommendations regarding this conflicting issue.

Search Criteria

Observational Studies

Systemic searches of PUBMED electronic database for published observational studies that reported baseline BP and early (<3 months) outcome (death, dependency, death or dependency, recurrent stroke, early neurological deterioration) were made by K.S. and G.T. The search strategy included the following key words: blood pressure, hypertension, acute, stroke, outcome, prognosis, death,

mortality, intracerebral haemorrhage. Additional studies were also sought from references of identified studies and reviews [15–20]. Functional status in the identified studies was typically assessed by the modified Rankin Scale (mRS) and the Barthel Index (BI). Early neurological deterioration in the identified studies was invariable measured with the National Institutes of Health Stroke Scale (NIHSS), the Canadian Stroke Scale (CSS) and the Canadian Neurological Score (CNS). Published reports that presented insufficient data, used other outcome measures or were duplicate articles were excluded. Decisions on inclusion and exclusion of the observational studies were made by consensus of the three authors

Intervention Trials

Intervention trials (pilot preliminary trials, safety and feasibility studies and randomised controlled trials) that assessed the effect of BP-lowering medications during the first 2 weeks after stroke onset on early (<3 months) outcome were identified through systematic searches of PUBMED and Cochrane electronic databases by K.S. and G.T. The search strategy included the following key words: blood pressure, hypertension, acute, stroke, intracerebral haemorrhage, blood pressure lowering, blood pressure reduction, blood pressure elevation, induced hypertension, pilot trial, safety study, randomised controlled trial. Additional studies were also sought from references of identified studies and reviews [15–20]. Studies that evaluated the impact of BP reduction after the second week of ictus on secondary prevention of stroke and other vascular events were excluded. Published reports that were duplicate articles were not included in the present review. Decisions on inclusion and exclusion of the interventional trials were made by consensus of the three authors.

Table 1. Observational studies investigating the relationship between initial blood pressure (BP) values and short-term outcome (≤ 3 months) in patients with acute ischaemic stroke (IS)

Study	Year	n	BP timing	BP method	Results
Sacco et al. [36]	1989	1,273	admission (<7 days)	not given	DBP ≥ 100 mm Hg associated with increased 1-month stroke recurrence
Davalos et al. [74]	1990	98	admission (<8 h)	not given	increased SBP associated with early (within first 48 h) neurological deterioration (CNS, linear relationship)*
Carlberg et al. [75]	1993	831	admission (<1 week)	manual	(a) patients with impaired consciousness: Increased MAP was associated with 1-month M (linear relationship)* (b) alert patients: no association between BP and outcome
Toni et al. [76]	1995	152	admission (<5 h)	not given	(a) no association between BP and progressing neurological deficit (b) no association between BP and 1-month M/D
Finocchi et al. [77]	1996	351	admission (<48 h)	manual	no association between BP and 1-month M/D

Table 1 (continued)

Study	Year	n	BP timing	BP method	Results
Chamorro et al. [78]	1998	481	repeated recordings over 7 days following admission	manual	moderate (20–30%) drop in MAP on day 2 after stroke onset was associated with complete functional recovery (mRS) at 1 week
Dawson et al. [68]	2000	92	<72 h from ictus	manual and beat-to-beat recordings***	increased beat-to-beat MAP and MAP variability was associated with 1-month M/D (linear relationship)*
Ahmed et al. [79]	2001	92**	Time of randomisation (<24 h)	not given	increased BP categorised at different BP levels was associated with 21-day M/D
Bhalla et al. [80]	2001	70	<24 h	manual and ABPM	(a) no association between casual and 24-hour SBP/DBP and functional status at 1 week (b) increased day to night time BP change was associated with complete functional recovery (mRS) at 1 week
Boreas et al. [81]	2002	403	repeated recordings over 4 days following admission (24 h)	manual	(a) no association between admission SBP/DBP and outcome (b) night-time SBP ≥ 165 mm Hg and night-time DBP ≤ 60 mm Hg were associated with 3-month M/D (c) decrease in daytime DBP (between day 0 and day 4) ≥ 10 mm Hg was associated with 3-month M/D
Leonardi-Bee et al. [31]	2002	17,398	admission (<48 h)	not given	(a) 14-day M increased for every 10 mm Hg ≤ 150 mm Hg and for every 10 mm Hg >150 mm Hg (U-shaped relationship) (b) increased SBP associated with 14-day stroke recurrence (linear relationship)
Aslanyan et al. [82]	2003	1,455	repeated recordings over 60.25 h following admission (<6 h of ictus)	manual	increased weighted average MAP associated with 3-month M, poor neurological (NIHSS) and functional status (BI) at 1 month (linear relationship)*
Oliveira-Filho et al. [25]	2003	115	repeated recordings over 24 h following admission (<24 h of ictus)	manual	SBP reduction within 24 h following admission was associated with increased 3-month M/D (linear relationship)*
Robinson et al. [69]	2003	124	admission (<24 h)	manual and ABPM	no association between admission and 24-hour BP and 1-month M/D
Semplicini et al. [83]	2003	92	repeated recordings over 7 days following admission (<6 h of ictus)	manual	increased admission MAP was associated with better neurological outcome (NIHSS-score) at 1 week (linear relationship)*
Vlcek et al. [84]	2003	372	preadmission, admission (<48 h of ictus), 1st day of ictus	manual	DBP decrease >25% during the 1st day was associated with increased D at day 5
Castillo et al. [25]	2004	304	repeated recordings over 7 days following admission (<24 h of ictus)	manual	reduction in SBP >20 mm Hg within 24 h following admission was associated with early (<48 h) neurological deterioration (CSS), increased infarct volume and 3-month M
Vemmos et al. [44]	2004	930	admission (<24 h)	manual	1-month M increased for different SBP levels below and above 121–140 mm Hg and for different DBP levels below and above 81–90 mm Hg (U-shaped relationship)
Okumura et al. [45]	2005	1,004	admission (<24h)	manual	1-month M increased for different SBP levels below and above 150–169 mm Hg and for different DBP levels below and above 100–109 mm Hg (U-shaped relationship)
Rodriguez-Garcia et al. [85]	2005	434	admission (<24 h)	manual and ABPM	(a) 24-hour SBP >160 mm Hg was associated with increased M/D at 1 week (b) SBP reduction >5 mm Hg at day 7 was associated with functional improvement (mRS)
Stead et al. [86]	2005	357	emergency department (<24 h)	manual	SBP <155 mm Hg (vs.155–220 mm Hg), DBP <70 mm Hg (vs.70–105 mm Hg), MAP <100 mm Hg (vs.100–140 mm Hg) associated with 3-month M

Studies including both patients with IS and ICH that did not analyse separately the relationship of acute BP with outcome for each stroke subtype were excluded.

ABPM = Ambulatory blood pressure monitoring (intermittent oscillometric recordings); BI = Barthel index; CNS = Canadian neurological scale; NIHSS = National Institutes of Health Stroke Scale; D = dependency (assessed by the modified Rankin scale, mRS); M = mortality.

* BP data were entered in the analyses as continuous variables; ** only the placebo-treated patients were included in the present table; *** non-invasive beat-to-beat blood pressure monitoring was used.

Table 2. Observational studies investigating the relationship between initial blood pressure (BP) values and short-term outcome (≤ 3 months) in patients with acute intracerebral haemorrhage (ICH)

Study	Year	n	BP timing	BP method	Results
Dunne et al. [87]	1987	75 (CBL)	admission	not given	SBP > 200 associated with 6-day M/D
Broderick et al. [88]	1993	188	admission	not given	no association between admission BP and 1-month M
Carlberg et al. [75]	1993	85	admission (<1 week)	manual	(a) patients with impaired consciousness: Increased MAP was associated with 1-month M (linear relationship)* (b) alert patients: no association between BP and outcome
Dandapani et al. [89]	1995	87	repeated recordings over 6 h following admission	not given	(a) MAP >145 mm Hg (0–2 h) was associated with 1-month M (b) MAP >125 mm Hg (2–6 h) was associated with 1-month M
Qureshi et al. [90]	1995	182	emergency department	manual	no association between MAP and early deterioration or in-hospital M
Folgelholm et al. [91]	1997	282 (SPT)	repeated recordings over the first 24 h	manual	increased MAP was associated with 28-day M (linear relationship)*
Terayama et al. [92]	1997	1,701	admission (<24 h)	not given	(a) thalamic and putaminal PICH = higher MAP in patients who died during hospitalization (b) subcortical, pontine and CBL PICH: no association between MAP and outcome
Leira et al. [93]	2004	266 (SPT)	repeated recordings over the first 48 h following admission (<12 h)	manual	(a) increased highest SBP associated with early (within first 48 h) neurological deterioration (CSS, linear relationship)* (b) no association between BP and D
Vemmos et al. [44]	2004	191	admission (<24 h)	manual	1-month M increased for different SBP levels below and above 141–160 mm Hg and for different DBP levels below and above 101–110 mm Hg (U-shaped relationship)
Okumura et al. [45]	2005	1,097	admission (<24 h)	manual	1-month M increased for different SBP levels below and above 150–169 mm Hg (J-shaped relationship) and for different DBP levels below and above 90–99 mm Hg (U-shaped relationship)

Studies including both patients with IS and ICH that did not analyse separately the relationship of acute BP with outcome for each stroke subtype were excluded.

BI = Barthel index; CBL = cerebellar; STN = supratentorial CSS = Canadian stroke scale; D = dependency (assessed by the modified Rankin scale, mRS); M = mortality.

* BP data was entered in the analyses as continuous variables.

Results

Lowering Blood Pressure in Acute Stroke

Contras

Ischaemic Stroke

There is a series of arguments against treating hypertension in IS: (1) In the natural course of the disease BP values tend to normalise spontaneously within hours or days after IS onset [7, 13, 21, 22]. (2) Since the rescue of tissue at risk remains the main goal of acute IS treatment, keeping tissue perfusion pressure above a critical level

within the ischaemic penumbra becomes of crucial importance. It is well known that cerebral autoregulation normally maintains perfusion over a wide range of systemic BP (fig. 1) and its curve is shifted towards higher BP values in chronic hypertensive individuals. During the acute phase of IS, cerebral autoregulation becomes dysfunctional and perfusion tends to be passively dependent on perfusion pressure [23]. Hence, it has been reasoned that BP should not be actively lowered in order to avoid any further reduction of the cerebral blood flow, with the possible sequelae of infarct extension and worsening of outcome [15, 24]. The degree of BP reduction in the first

Fig. 1. Relationship between cerebral blood flow and mean arterial pressure under normal conditions and in ischaemia.

24 h after stroke onset was independently associated with poor outcome in a series of patients with IS, who received antihypertensive treatment (59%) in the emergency department [25]. Moreover, it has been recently reported that a BP drop >20 mm Hg during the first hours of ictus, followed by the use of BP-lowering medications, was the most important prognostic factor for early neurological deterioration, increased infarct volume and mortality at 3 months [26]. Furthermore, the investigators of Intravenous Nimodipine West European Trial have demonstrated that aggressive BP reduction with high-dose intravenous nimodipine was associated with neurological worsening of acute stroke patients [27, 28]. The authors assumed that the profound DBP drop (>20%) in patients with already altered autoregulation may cause a further decrease in cerebral perfusion pressure and regional blood flow with deterioration of collateral supply below the lethal thresholds in the area of the ischaemic penumbra. (3) The course of elevated systolic BP in patients undergoing intra-arterial thrombolysis is inversely associated with the degree of vessel recanalisation. In a recent study, Mattle et al. [29] reported that, in patients where thrombolysis succeeded to reopen the occluded vessel, which was responsible for tissue ischaemia, SBP declined significantly faster in comparison to cases where recanalisation had failed. Based on the former observations it may be postulated that BP elevation might be a compensatory reaction to persistent vessel occlusion.

Intracerebral Haemorrhage

The following arguments are in favour of not treating hypertension in the acute stage of ICH: (1) In the natural course of the disease increased BP declines to baseline values within the first days after ICH onset [7, 30]. (2) A zone of hypoperfusion in brain surrounding acute ICH has been reported in positron emission tomography (PET) studies [31, 32]. Consequently, it has been argued that overaggressive BP reduction has the potential to further decrease the cerebral perfusion pressure and theoretically worsen brain injury particularly in the setting of increased intracranial pressure [23]. The findings of a single-photon emission CT (SPECT) study demonstrating that drug-induced reductions of mean arterial pressure (MAP) in excess of 20% during the acute period of the ICH resulted in a decrease of regional cerebral blood flow (rCBF) are in keeping with the former hypothesis [33].

Pros

Ischaemic Stroke

The following arguments support the therapeutic manipulation of BP in the acute IS stage: (1) High BP levels in acute IS have been associated with subsequent death or dependency in a recent meta-analysis of observational studies investigating the association of BP with outcome [19]. (2) Sustained high BP values, assessed by means of ambulatory blood pressure monitoring have been associated with subsequent oedema formation [34], whereas casually documented elevated BP values have also been related to death resulting from presumed cerebral oedema in acute IS patients according to the results of the International Stroke Trial (IST) [35]. (3) Data from observational studies have suggested that increased admission BP values are related to early [35, 36] and late [37, 38] stroke recurrence.

Intracerebral Haemorrhage

Antihypertensive treatment is considered in patients with acute ICH on the basis of the subsequent arguments: (1) High BP levels in acute ICH have been associated with subsequent death, death or dependency and death or deterioration in a recent meta-analysis of observational studies investigating the association of BP with outcome [19]. (2) Increased acute BP values assessed by means of ambulatory blood pressure monitoring have been associated with cerebral oedema in ICH patients [14]. (3) Elevated BP values during the acute stroke stage have been shown to increase the risk of haematoma enlargement in patients with ICH [19, 39, 40]. (4) High admission BP values during the acute stage of ICH have been related to an increased rate of recurrent haemorrhagic stroke [41].

The U-Shaped Relationship between Acute BP Values and Stroke Outcome

Ischaemic Stroke

Some of the former pathophysiological facts and study findings support on the one hand the thesis of not applying – or even discontinuing previously initiated – antihypertensive treatment in the acute phase of stroke in order to avoid further infarct expansion and tissue necrosis. On the other hand, there is solid evidence suggesting that moderate BP lowering might be beneficial by reducing the risk of oedema formation, haematoma enlargement and stroke recurrence, improving this way survival and clinical outcome. Because of these conflicting issues and the lack of unambiguous data, the appropriate evidence-based approach to post-stroke hypertension remains to be settled [42, 43].

The U-shaped relationship between acute BP values and IS outcome might be an explanation for the discrepancy of findings and arguments. The IST was the first to demonstrate a U-shaped relationship between baseline SBP and both early death and late death or dependency in patients with IS [35]. Both high and low SBP values were independent prognostic factors for poor clinical outcome. This seemed to be attributed to the higher rates of early recurrence and cerebral oedema among patients with high BP, while low BP values (SBP <120 mm Hg) in the acute stroke setting have been associated with a severe clinical stroke (total anterior circulation syndrome) and an excess of deaths due to coronary heart disease [35]. Additionally, both low and high admission SBP and DBP values have been related to increased infarct volume [26]. A similar U-shaped relationship between admission SBP and DBP levels and early mortality among patients with acute IS has also been documented by two recent studies [44, 45]. The best outcome was observed in patients with normal or mildly elevated admission SBP (U point or nadir of the curve: 121–170 mm Hg) and DBP values (U point or nadir of the curve: 81–110 mm Hg), suggesting that both extremely high and low admission BP values are likely to affect outcome adversely.

Intracerebral Haemorrhage

The U-shaped curve relating acute BP values with outcome has also been confirmed in patients with ICH according to the results of a Greek [44] and a Japanese [45] hospital-based study, which demonstrated that both lower and higher BP levels following ICH were predictors for poor early prognosis.

Interpretation of Existing Trial Data

Ischaemic Stroke

Unfortunately, solid data from randomised controlled trials (RCTs) are limited and inconclusive when considering whether lowering BP during the first hours of ictus is beneficial or not in IS patients. More specifically no randomised data exist for central acting agents, alpha adrenergic receptor blockers or other vasodilators, such as hydralazine. The efficacy and safety of transdermal nitric oxide donors has been demonstrated by a small RCT that studied transdermal glyceryl trinitrate and found that it lowered BP by 5–8% in a stroke population that mainly consisted of patients with recent IS (33 of the 37 cases) [46]. A recent pilot RCT concluded that following acute IS, oral benflurazide, a thiazide diuretic, did not lower systemic BP levels over the subsequent 7-day period [47].

Though the Perindopril Protection Against Recurrent Stroke Study [48] and the Heart Outcomes Prevention Evaluation-HOPE [49] have evaluated the efficacy of perindopril and ramipril, respectively, in the risk reduction of recurrent stroke in patients with cerebrovascular disease, neither of these studies provides information that might help us to determine how acutely following stroke the angiotensin-converting enzyme inhibitors can be commenced safely. One small RCT found that oral perindopril reduced BP values by 11% without altering global cerebral blood flow or middle cerebral artery (MCA) blood flow velocity [50]. The Acute Candesartan Cilexetil Therapy in Stroke Survivors – ACCESS, a prospective double-blind, placebo-controlled, randomised phase II trial, evaluated the use of an angiotensin II receptor blocker in acute IS patients with severely elevated BP levels (SBP >180 mm Hg and/or DBP >105 mm Hg). Preliminary data from 342 patients demonstrated that oral candesartan reduced a composite secondary outcome (all-cause mortality and vascular events) by 52.5% [51]. It should be noted though that the trial was stopped prematurely with a neutral finding for its primary outcome (total mortality and disability at 3 months). Moreover, this preliminary observation remains to be confirmed by a larger phase III RCT [52].

In contrast, beta-blockers, such as propranolol and atenolol achieve a greater BP fall compared to placebo, but are characterised by a trend towards a worse outcome [20, 53]. The safety and feasibility of labetalol, a combined beta- and alpha-adrenergic antagonist, in rapidly and effectively reducing BP has been demonstrated in the NINDS thrombolysis trial [54]. Finally, the application of calcium channel antagonists during the acute stage of IS has no positive or negative effect on functional outcome

or survival, according to a review of 29 RCTs [55] and the conclusions of a review from the Blood Pressure in Acute Stroke Collaboration (BASC) [20]. In addition, the INWEST trial demonstrated that the functional outcome was worsened in parallel with the degree by which BP was reduced [27, 28].

Intracerebral Haemorrhage

The existing trial data in the ICH subgroup is even scarcer. In a small survey of 10 critically ill haemorrhagic stroke patients (7 cases with ICH and 3 cases of subarachnoid haemorrhage) treated in a surgical intensive unit labetalol infusion produced a rapid and mild BP-lowering effect (SBP reduction ranging between 6 and 19%, DBP reduction ranging between 3 and 26%). This response did not worsen perceived mental status or stroke-induced neurologic deficits [56]. Nishiyama et al. [57] determined the effect of nicardipine infusion (titrated to maintain SBP levels between 120–160 mm Hg) on intracranial pressure, MCA flow velocity as well as the presence of brain oedema and haematoma rebleeding in 22 patients with putaminal ICH after surgical evacuation. Intracranial pressure decreased during the infusion without any change in MCA velocity or any evidence of rebleeding and exacerbation of cerebral oedema. Powers et al. [58] had also evaluated the impact of BP reduction in 14 patients with acute (6–22 h after onset) supratentorial ICH on rCBF measured by means of PET scan. MAP was reduced by 15% using either nicardipine or labetalol infusions. Interestingly, no significant difference in the perihematoma rCBF or global CBF before and after treatment was observed. Lastly, Qureshi et al. [59] performed a multicenter prospective observational study to evaluate the feasibility and safety of intravenous antihypertensive protocol (infusion of labetalol and/or hydralazine and/or nitroprusside) for controlling SBP and DBP levels below 160 and 90 mm Hg, respectively, in 27 patients with acute ICH. The investigators documented a low rate of neurological deterioration (7.4%) and haematoma expansion (9.1%) in the treated patients. Furthermore, they noted that patients treated within 6 h from symptom onset were more likely to be functionally independent at 1 month compared with cases who were treated during the time window between 6 and 24 h.

Ongoing Trials

The results of currently ongoing trials may provide some answers to some of the former unresolved issues. The Control of Hypertension and Hypotension Immediately Post-Stroke Trial [60] is a randomised double-blind

placebo-controlled study using stepwise angiotensin-converting enzyme inhibitors. Death and dependency at 2 weeks after stroke will be the primary outcome measure. The transdermal application of glyceryl trinitrate is evaluated in the Efficacy of Nitric Oxide in Stroke – ENOS – study [61]. Useful data about stroke patients who are already on antihypertensive medication are expected from the Continue or Stop Post-Stroke Antihypertensive Collaborative Study [62].

Raising Blood Pressure in Acute Stroke

Ischaemic Stroke

Feasibility, Safety and Preliminary Results of Induced BP Elevation. If BP lowering in the acute setting of stroke could have detrimental results, it could then be theoretically assumed that raising BP might be beneficial, especially in terms of saving tissue in the ischaemic penumbra. However, there is scarce randomised or observational evidence to support this practice. Rodorf et al. [63, 64] have reported that intravenous application of phenylephrine is safe and feasible based on the findings of two small pilot studies. Moreover, the investigators noted that the responders to vasopressors scored better in the NIHSS at discharge [64]. Norepinephrine infusion has also been used to induce hypertension in 19 acute IS patients with complete or subtotal MCA stroke and was associated with enhanced cerebral perfusion without any detrimental increases in intracranial pressure [65].

Selection of Candidate Patients for Induced BP Elevation. The results of a preliminary study showed that patients who were most likely to display functional gains with pressor therapy, were those with severe stenosis or occlusion of an internal carotid artery (ICA) and/or a MCA [64]. It is conceivable that induced BP elevation could be more beneficial in such cases, since the former stroke subgroup is the most likely to present with the largest perfusion-diffusion mismatch during the first hours of ictus. Furthermore, in an ambulatory BP-monitoring study that evaluated the early spontaneous time course of BP in IS subgroups of different etiology, a substantially steeper BP decline was documented in the large-artery-atherosclerotic stroke subgroup [14]. Finally, according to a recent pilot RCT pharmacological BP elevation in patients with acute IS and large perfusion-diffusion mismatch caused by occlusion or stenosis of ICA and/or MCA resulted in smaller tissue lesions, as these were visualised by means of perfusion weighted MRI on the third day after stroke onset [66]. The previous encouraging

findings warrant a full-scale double-blind clinical trial to investigate the efficacy and risks of this type of intervention specifically in the subgroup of patients with carotid artery disease.

Intracerebral Haemorrhage

To the best of our knowledge no study had previously addressed the issue of raising low or normal BP levels in the setting of acute ICH.

Discussion

Limitations and Shortcomings of Observational Studies

The discrepancies between the results of the various observational studies may reflect underlying methodological problems such as BP levels measured by different observers, retrospective BP documentation and lack of data on how BP was recorded. As illustrated in tables 1 and 2, the variation in the time of BP measurements (ranging from a few hours to several days after stroke onset) may also account in part for the conflicting results. In addition, certain reports did not investigate the relationship of acute BP levels with stroke outcome separately in the IS and the ICH subgroup, others used highly selected patient groups participating in clinical trials [27, 28], while some investigators continued or initiated BP-lowering medications following admission [25, 26]. Furthermore, the study protocol of certain reports did not include CT scans routinely in all stroke patients [7, 67], while in a number of studies unconscious stroke patients and cases with atrial fibrillation were excluded [67–69]. Besides, functional disability and neurological impairment were evaluated by different outcome measures in the majority of the observational studies (tables 1, 2). Finally, in the IST, which is the study that involved by far the largest cohort of patients ($n = 17,398$), only a single measure of SBP was available for each patient [35]. Consequently, the relationship of DBP and its derivatives (MAP, pulse pressure) with outcome could not be evaluated.

Limitations and Shortcomings of Intervention Trials *Ischaemic Stroke*

Certain limitations of the pilot trials that assessed antihypertensive treatment strategies in acute IS patients are worth pondering. For one, the time window for randomisation ranged from 24 [51] to 120 h [46] following stroke onset in these preliminary intervention studies. Consequently, the different degrees of BP reduction document-

ed in the various antihypertensive drug classes should be acknowledged after taking into account the former confounder. Moreover, only in the ACCESS study all subjects received carotid ultrasound examination before randomisation, which resulted in the exclusion of subjects with severe stenosis and occlusion of the ICA [51]. Since patients with carotid artery disease present the highest perfusion-diffusion mismatch, even moderate BP reductions may result in substantial reductions in CBF and cause infarct expansion [24]. This safety issue should be taken into consideration in the design of future phase III trials. It is also noteworthy that during the placebo-controlled phase of the ACCESS study in the first 7 days following recruitment, BP levels were similar in patients treated with angiotensin II receptor blockers and patients receiving placebo. Consequently, the authors assumed that the beneficial effect of candesartan could be attributed to its neurohumoral inhibiting effects [51]. Further research is needed to resolve the underlying mechanisms by which angiotensin receptor blockers affect the cerebrovascular system. Finally, Doppler data in the majority of intervention trials [47, 50] support the hypothesis that a number of BP-lowering medications does not adversely affect CBF or alter cerebral haemodynamics in a clinically significant way. Other forms of brain imaging techniques such as SPECT or PET scanning are needed to further validate the previous findings and provide additional information on the effects of BP-lowering treatment on regional perfusion, particularly in the area surrounding the cerebral infarct.

Limited preliminary trials seem to support the alternative therapeutic approach of induced hypertension in specific subgroups of acute IS patients. Nevertheless, there are important arguments against raising BP during the acute IS stage. Although, drug-induced hypertension holds promise, this therapy may be associated with increased risk of brain oedema or haemorrhagic transformation of the cerebral infarction, while additional vasopressor-related complications may include cardiac ischaemia or arrhythmias [52]. Furthermore, it should be acknowledged that sympathomimetic agents tend to induce platelet activation, while it is noteworthy that the use of such drugs within nasal decongestants and in weight reduction programmes has been associated with the development of stroke and other vascular diseases [70]. Lastly, certain agents which raise BP (although this was not their intended effect) had unfavourable effects on stroke outcome in RCTs during the acute stroke period. More specifically, the administration of dapsirin cross-linked haemoglobin has been associated with raised BP levels during the first three days of ictus and worse outcome [71].

Table 3. Current guidelines for the management of blood pressure in the acute phase of ischaemic stroke

BP level, mm Hg	Treatment
<i>Stroke Council of the American Stroke Association</i> [43, 52]	
SBP $\leq$ 220 or DBP $\leq$ 120	(a) defer antihypertensive therapy (b) drug-induced hypertension is not recommended for the treatment of most patients.
SBP >220 or 121 < DBP < 140	(i) labetalol 10–20 mg i.v. over 1–2 min, may repeat or double every 10 min (maximum 300 mg) (ii) nicardipine 5 mg/h i.v. infusion as initial dose, titrate to desired effect by increasing 2.5 mg/h every 5 min (maximum 15 mg/h) target: 10–15% reduction of BP
DBP >140	(i) nitroprusside 0.5 μ g/kg/min as initial dose with continuous BP monitoring target: 10–15% reduction of BP
<i>European Stroke Initiative</i> [72]	
180 < SBP < 220 and/or 105 < DBP < 140	defer antihypertensive therapy
SBP > 220 or 121 < DBP < 140 on repeated measures	(i) labetalol 5–20 mg i.v. (ii) uradipil 10–50 mg i.v., followed by 4–8 mg/h i.v. (iii) captopril 6.25–12.5 mg p.o. or i.m. (iv) clonidine 0.15–0.30 mg i.v. or s.c. (v) dihydralazine 5 mg i.v. plus metoprolol 10 mg
DBP >140	(i) sodium nitroprusside 1–2 mg (ii) nitroglycerin 5 mg i.v., followed by 1–4 mg/h i.v.

Intracerebral Haemorrhage

Certain important methodological issues should be addressed before interpreting the results of the trials that investigated the feasibility of BP-lowering medications in the setting of acute ICH. First, the rates of neurological deterioration and haematoma expansion were compared to unmatched patients with variable characteristics. Therefore, no direct comparisons can be made. Second, the small number of patients enrolled in the former studies raises concerns regarding the safety of aggressive pharmacological treatment of acute hypertension, especially after taking into consideration that nicardipine infusion was associated with decreased cerebral perfusion pressure in one trial [57], although the former reduction did not correlate with a poorer outcome. Third, there is a possibility that asymptomatic haematoma expansion may be undetected in certain cases, since repeat CT scans were not acquired consistently but at the discretion of treating physicians and were usually performed only in patients with clinical deterioration [59].

Recommendations – Conclusions

Ischaemic Stroke

The European Stroke Initiative (EUSI) [72] and the Stroke Council of the American Stroke Association [43,

52] have released updated scientific statements and guidelines regarding the management of hypertension in the setting of acute IS. Both authorities recommend that BP should not be lowered in IS patients who are not otherwise candidates for thrombolysis (grade C recommendation; supported by data from non-randomised concurrent cohort studies with historical controls or anecdotal case series). Threshold BP values demanding immediate medical interventions are recommended by consensus (table 3). More specifically, pharmacological intervention is indicated if repeated BP readings reveal SBP values >220 mm Hg and DBP >120 mm Hg. In patients eligible for thrombolytic therapy SBP values >185 mm Hg or DBP values >110 mm Hg should be actively treated and maintained at desired levels (<185/110 mm Hg) during and after rt-PA infusion. Situations that might require urgent antihypertensive therapy independent of BP levels include acute myocardial infarction, severe left ventricular heart failure, aortic dissection, acute renal failure, acute pulmonary oedema and hypertensive encephalopathy (table 4).

In cases where acute therapeutic manipulation of BP is indicated, BP lowering should be done cautiously at a clinically significant and relevant degree (target of BP reduction ranging from 10 to 15%), in order to avoid profound

(>20%) BP reductions that have been associated with neurological and functional worsening [27]. Parenteral agents such as labetalol, nicardipine or uradipil that are easily titrated and have minimal vasodilatory effects on cerebral blood flow are preferred (table 3). In certain cases with excessive DBP levels (>140 mm Hg), intravenous administration of sodium nitroprusside is recommended for adequate BP control, despite possible major adverse effects, such as reflex tachycardia and coronary artery ischaemia. The use of sublingual nifedipine should be avoided because of the risk of abrupt BP reduction and possible ischaemic steel [43, 72]. Finally, at present, drug-

induced hypertension cannot be recommended for the treatment of most patients with IS [52].

Intracerebral Haemorrhage

Current recommendations for treatment of elevated BP levels in patients with acute ICH are more aggressive than those for cases with IS [42]. Accordingly, SBP and DBP levels should be maintained below 180 and 105 mm Hg, respectively (table 5). If antihypertensive treatment is indicated during the acute stage of ICH, then BP should be lowered carefully in a monitored setting with close and continuous observation of BP values and using an easily titratable, short-acting agent (such as labetalol, esmolol, enalapril or nicardipine). Theoretical concerns regarding the vasodilatory effects of sodium nitroprusside and its potential detrimental impact on intracranial pressure [73] limit its use only in patients with excessively high SBP (>230 mm Hg) and DBP (>140 mm Hg) levels. Extreme (>20%) reductions in BP levels ought to be avoided [32] and if SBP falls below 90 mm Hg the use of pressors is indicated [42].

Perspectives

In the absence of solid data supporting the elevation or reduction of BP in patients with acute stroke, it is clear that evidence from RCTs is urgently required. These trials should have sufficient power and size to take into account:

Table 4. Indications for urgent antihypertensive therapy in patients with acute ischaemic stroke according to current guidelines

Authority	Urgent treatment indications
Stroke Council of the American Stroke Association [43]	acute myocardial infarction acute renal failure aortic dissection acute pulmonary oedema hypertensive encephalopathy
European Stroke Initiative [72]	acute myocardial ischaemia acute renal failure aortic arch dissection cardiac insufficiency

Table 5. Current guidelines for the management of blood pressure in the acute phase of intracerebral haemorrhage [42]

BP level, mm Hg	Treatment
SBP <90	(a) volume replenishment (isotonic saline or colloids) as first-line approach (b) infusion of pressors (if hypotension persists after correction of volume deficit) as second-line approach: (i) phenylephrine 2–10 µg/kg/min i.v. (ii) dopamine 2–20 µg/kg/min i.v. (iii) norepinephrine 0.05–0.20 µg/kg/min i.v.
SBP = 91 – 179 and DBP <105	defer antihypertensive therapy
180 < SBP < 230 or 105 < DBP < 140 (2 readings 20 min apart)	(i) labetalol 5–100 mg i.v. by intermittent bolus doses of 10–40 mg or continuous drip (2–8 mg/min) (ii) esmolol 500 µg/kg i.v. loading dose; maintenance use 50–200 µg/kg/min (iii) enalapril 0.625–1.2 mg i.v. (iv) other easily titratable i.v. medications (diltiazem, lisinopril, verapamil, nicardipine)
SBP > 230 or DBP > 140 (2 readings 5 min apart)	(i) nitroprusside 0.5–1.0 µg/kg/min i.v.

- (1) different patient groups according to age, gender, stroke subtypes; comorbidities; (2) different treatment paradigms (increase or decrease BP, drug class, timing and route of therapeutic BP manipulation, continue or temporarily stop prior antihypertensive medications); (3) different treatment effects of antihypertensive drug classes (BP reduction, neurohumoral inhibitory effects); (4) other acute stroke treatment strategies (thrombolysis); (5) strict, clinically meaningful outcome measures, and
- (6) safety issues. Smaller studies are also needed to investigate the impact of vasoactive drugs in pathophysiological mechanisms underlying stroke, such as cerebral perfusion and haemostasis. The anticipated results of the currently ongoing phase III trials may clarify certain of the former issues regarding the optimal BP management in acute stroke and provide adequate scientific basis for more evidence-based treatment decisions in the moderately near future.

References

- 1 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R: Prospective studies collaboration: age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–1913.
- 2 Chalmers J, Todd A, Chapman N, et al: International Society of Hypertension Writing Group. International Society of Hypertension Writing Group. International Society of Hypertension (ISH): statement on blood pressure lowering and stroke prevention. *J Hypertens* 2003;21:651–663.
- 3 Donnan GA, Davis SM, Thrift A: The role of blood pressure lowering before and after stroke. *Curr Opin Neurol* 2003;16:81–86.
- 4 Rashid P, Leonardi-Bee J, Bath P: Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. *Stroke* 2003;34:2741–2748.
- 5 CAST (Chinese Acute Stroke Trial) Collaborative Group: (CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet* 1997;349:1641–1649.
- 6 International Stroke Trial Collaborative Group: The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischaemic stroke. *Lancet* 1997;349:1569–1581.
- 7 Britton M, Carlsson A, de Faire U: Blood pressure course in patients with acute stroke and matched controls. *Stroke* 1986;17:861–864.
- 8 Myers MG, Norris JW, Hachinski VC, Sole MJ: Plasma norepinephrine in stroke. *Stroke* 1981;12:200–204.
- 9 Olson T, Marklund N, Gustafson Y, Nasman B: Abnormalities at different levels of the hypothalamic-pituitary adrenocortical axis early after stroke. *Stroke* 1992;23:1573–1576.
- 10 Carlberg B, Asplund K, Hagg E: High blood pressure in acute stroke – is it white coat hypertension? *J Intern Med* 1990;228:291–292.
- 11 Ito A, Omae T, Katsuki S: Acute changes in blood pressure following vascular diseases in the brain stem. *Stroke* 1973;4:80–84.
- 12 Harper G, Castleden CM, Potter JF: Factors affecting changes in blood pressure after acute stroke. *Stroke* 1994;25:1726–1729.
- 13 Vemmos KN, Tsivgoulis G, Spengos K, et al: Blood pressure course in acute ischaemic stroke varies in relation to stroke subtype. *Blood Press Monit* 2004;9:107–114.
- 14 Vemmos K, Spengos K, Tsivgoulis G, et al: Factors influencing acute blood pressure values in stroke subtypes. *J Hum Hypertens* 2004;18:253–259.
- 15 Yatsu FM, Zivin J: Hypertension in acute ischemic strokes: not to treat. *Arch Neurol* 1985;42:999–1000.
- 16 Spencer JD: Hypertension in acute ischemic stroke: to treat. *Arch Neurol* 1985;42:1000–1002.
- 17 Robinson TG, Potter JF: Blood pressure in acute stroke. *Age Ageing* 2004;33:6–12.
- 18 Bath P, Chalmers J, Powers W, et al: International Society of Hypertension Writing Group. International Society of Hypertension (ISH): statement on the management of blood pressure in acute stroke. *J Hypertens* 2003;21:665–672.
- 19 Willmot M, Leonardi-Bee J, Bath PM: High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension* 2004;43:18–24.
- 20 Blood Pressure in Acute Stroke Collaboration (BASC): Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev* 2001;CD000039.
- 21 Broderick J, Brott T, Barsan W, et al: Blood pressure during the first minutes of focal cerebral ischemia. *Ann Emerg Med* 1993;22:1438–1443.
- 22 Carlberg B, Asplund K, Hagg E: Course of blood pressure in different subsets of patients after acute stroke. *Cerebrovasc Dis* 1991;1:281–287.
- 23 Powers WJ: Acute hypertension after acute stroke: the scientific basis for treatment decisions. *Neurology* 1993;43:461–467.
- 24 Fischberg GM, Lozano E, Rajamani K, Ameriso S, Fisher MJ: Stroke precipitated by moderate blood pressure reduction. *J Emerg Med* 2000;19:339–346.
- 25 Oliveira-Filho J, Silva SC, Trabuco CC, Pedreira BB, Sousa EU, Bacellar A: Detrimental effect of blood pressure reduction in the first 24 h of acute stroke onset. *Neurology* 2003;61:1047–1051.
- 26 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;35:520–526.
- 27 Wahlgren NG, MacMahon DG, de Keyser J, Indredavik B, Ryman T, INWEST Study Group: Intravenous Nimodipine West European Stroke Trial (INWEST) of nimodipine in the treatment of acute ischaemic stroke. *Cerebrovasc Dis* 1994;4:204–210.
- 28 Ahmed N, Nasman P, Wahlgren NG: Effect of intravenous nimodipine on blood pressure and outcome after acute stroke. *Stroke* 2000;31:1250–1255.
- 29 Mattle HP, Kappeler L, Arnold M, et al: Blood pressure and vessel recanalization in the first hours after ischemic stroke. *Stroke* 2005;36:264–268.
- 30 Morfis L, Schwartz RS, Poulos R, Howes LG: Blood pressure changes in acute cerebral infarction and hemorrhage. *Stroke* 1997;28:1401–1405.
- 31 Zazulia AR, Diringner MN, Videen TO, et al: Hypoperfusion without ischemia surrounding acute intracerebral hemorrhage. *J Cereb Blood Flow Metab*. 2001;21:804–810.
- 32 Videen TO, Dunford-Shore JE, Diringner MN, Powers WJ: Correction for partial volume effects in regional blood flow measurements adjacent to hematomas in humans with intracerebral hemorrhage: implementation and validation. *J Comput Assist Tomogr* 1999;23:248–256.
- 33 Kuwata N, Kuroda K, Funayama M, Sato N, Kubo N, Ogawa A: Dysautoregulation in patients with hypertensive intracerebral hemorrhage: a SPECT study. *Neurosurg Rev* 1995;18:237–245.

- 34 Vemmos K, Tsivgoulis G, Spengos K, et al: Association between 24-h blood pressure monitoring variables and oedema formation in patients with hyperacute stroke. *J Hypertens* 2003;21:2167–2173.
- 35 Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA, IST Collaborative Group: Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke* 2002;33:1315–1320.
- 36 Sacco RL, Foulkes MA, Mohr JP, Wolf PA, Hier DB, Price TR: Determinants of early recurrence of cerebral infarction. *The Stroke Data Bank*. *Stroke* 1989;20:983–989.
- 37 Hier DB, Foulkes MA, Swintoniowski M, et al: Stroke recurrence within 2 years after ischaemic infarction. *Stroke* 1991;22:155–161.
- 38 Tsivgoulis G, Spengos K, Zakopoulos N, Manios E, Vassilopoulos D, Vemmos K: Twenty-four-hour pulse pressure predicts long-term recurrence in acute stroke patients. *J Neurol Neurosurg Psychiatry* 2005;76:1360–1365.
- 39 Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T: Predisposing factors to enlargement of spontaneous intracerebral hematoma. *Stroke* 1997;28:2370–2375.
- 40 Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A: Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. *Stroke* 2004;35:1364–1367.
- 41 Arakawa S, Saku Y, Ibayashi S, Nagao T, Fujishima M: Blood pressure control and recurrence of hypertensive brain hemorrhage. *Stroke* 1998;29:1806–1809.
- 42 Broderick JP, Adams HP Jr, Barsan W, et al: Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1999;30:905–915.
- 43 Adams HP Jr, Adams RJ, Brott T, et al: Stroke Council of the American Stroke Association. Guidelines for the early management of patients with ischemic stroke: A scientific statement from the Stroke Council of the American Stroke Association. *Stroke* 2003;34:1056–1083.
- 44 Vemmos KN, Tsivgoulis G, Spengos K, et al: U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med* 2004;255:257–265.
- 45 Okumura K, Ohya Y, Maehara A, Wakugami K, Iseki K, Takishita S: Effects of blood pressure levels on case fatality after acute stroke. *J Hypertens* 2005;23:1217–1223.
- 46 Bath PMW, Pathansali R, Iddenden R, Bath FJ: The effect of transdermal glyceryl trinitrate, a nitric oxide donor, on blood pressure and platelet function in acute stroke. *Cerebrovasc Dis* 2001;11:265–272.
- 47 Eames PJ, Robinson TG, Panerai RB, Potter JF: Bendroflumazide fails to reduce elevated blood pressure levels in the immediate post-stroke period. *Cerebrovasc Dis* 2005;19:253–259.
- 48 PROGRESS Collaborative Group: Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033–1041.
- 49 Bosch J, Yusuf S, Pogue J, et al: HOPE Investigators. Heart outcomes prevention evaluation: use of ramipril in preventing stroke: double blind randomised trial. *Br Med J* 2002;324:699–702.
- 50 Dyker AG, Grosset DG, Lees K: Perindopril reduces blood pressure but not cerebral blood flow in patients with recent cerebral ischemic stroke. *Stroke* 1997;28:580–583.
- 51 Schrader J, Luders S, Kulschewski A, et al: Acute Candesartan Cilexetil Therapy in Stroke Survivors Study Group (2003). The ACCESS Study: evaluation of acute candesartan cilexetil therapy in stroke survivors. *Stroke* 2003;34:1699–1703.
- 52 Adams H, Adams R, Del Zoppo G, Goldstein LB: Stroke Council of the American Heart Association; American Stroke Association (2005). Guidelines for the early management of patients with ischemic stroke: 2005 guidelines update a scientific statement from the Stroke Council of the American Heart Association/American Stroke Association. *Stroke* 2005;36:916–923.
- 53 Barer DH, Cruickshank JM, Ebrahim SB, Mitchell JR: Low dose beta blockade in acute stroke ('BEST' trial): an evaluation. *Br Med J* 1998;296:737–741.
- 54 Brott T, Lu M, Kothari R, et al: Hypertension and its treatment in the NINDS rt-PA Stroke Trial. *Stroke* 1998;29:1504–1509.
- 55 Horn J, Limburg M: Calcium antagonists for ischemic stroke: a systematic review. *Stroke* 2001;32:570–576.
- 56 Patel RV, Kertland HR, Jahns BE, Zarowitz BJ, Mlynarek ME, Fagan SC: Labetalol: response and safety in critically ill hemorrhagic stroke patients. *Ann Pharmacother* 1993;27:180–181.
- 57 Nishiyama T, Yokoyama T, Matsukawa T, Hanaoka K: Continuous nicardipine infusion to control blood pressure after evacuation of acute cerebral hemorrhage. *Can J Anaesth* 2000;47:1196–1201.
- 58 Powers WJ, Zazulia AR, Videen TO, et al: Autoregulation of cerebral blood flow surrounding acute (6 to 22 hs) intracerebral hemorrhage. *Neurology* 2001;57:18–24.
- 59 Qureshi AI, Mohammad YM, Yahia AM, et al: A prospective multicenter study to evaluate the feasibility and safety of aggressive antihypertensive treatment in patients with acute intracerebral hemorrhage. *J Intens Care Med* 2005;20:34–42.
- 60 Potter J, Robinson T, Ford G, et al: The CHHIPS Trial Group. CHHIPS (Controlling Hypertension and Hypotension Immediately Post-Stroke) Pilot Trial: rationale and design. *J Hypertens* 2005;23:649–655.
- 61 Bath PM, Willmot MR, Weaver C, Leonardi-Bee J: Efficacy of nitric oxide in stroke (ENOS) trial – a prospective randomised controlled trial in acute stroke. *Cerebrovasc Dis* 2002;13(suppl 3):79.
- 62 COSSACS Trial Group: COSSACS (Continue or Stop Post-Stroke Antihypertensives Collaborative Study): rationale and design. *J Hypertens* 2005;23:455–458.
- 63 Rordorf G, Cramer SC, Efird JT, Schwamm LH, Buonanno FS, Koroshetz WJ: Pharmacological elevation of blood pressure in acute stroke: clinical effects and safety. *Stroke* 1997;28:2133–2138.
- 64 Rordorf G, Koroshetz WJ, Ezzeddine MA, Segal AZ, Buonanno FS: A pilot study of drug induced hypertension for treatment of acute stroke. *Neurology* 2001;56:1210–1213.
- 65 Schwarz S, Georgiadis D, Aschoff A, Schwab S: Effects of induced hypertension on intracranial pressure and flow velocities of the middle cerebral arteries in patients with large hemispheric stroke. *Stroke* 2002;33:998–1004.
- 66 Hillis AE, Ulatowski JA, Barker BP, 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;16:236–246.
- 67 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;7:264–272.
- 68 Dawson SL, Manktelow BN, Robinson TG, Panerai RB, Potter JF: Which parameters of beat-to-beat blood pressure and variability best predict early outcome after acute ischemic stroke? *Stroke* 2000;31:463–468.
- 69 Robinson TG, Dawson SL, Eames PJ, Panerai RB, Potter JF: Cardiac baroreceptor sensitivity predicts long-term outcome after acute ischemic stroke. *Stroke* 2003;34:705–712.
- 70 Kernan WN, Viscoli CM, Brass LM, et al: Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* 2000;43:1826–1832.
- 71 Saxena R, Wijnhoud AD, Carton H, et al: Controlled safety study of a hemoglobin-based oxygen carrier, DCLHb, in acute ischemic stroke. *Stroke* 1999;20:993–996.
- 72 Hacke W, Kaste M, Bogousslavsky J, et al: European Stroke Initiative Executive Committee and the EUSI Writing Committee. European Stroke Initiative Recommendations for Stroke Management – Update 2003. *Cerebrovasc Dis* 2003;16:311–337.
- 73 Cottrell JE, Patel K, Turndorf H, Ransohoff J: Intracranial pressure changes induced by sodium nitroprusside in patients with intracranial mass lesions. *J Neurosurg* 1978;48:329–331.
- 74 Davalos A, Cendra E, Teruel J, Martinez M, Genis D: Deteriorating ischemic stroke: risk factors and prognosis. *Neurology* 1990;40:1865–1869.

- 75 Carlberg B, Asplund K, Hagg E: The prognostic value of admission blood pressure in patients with acute stroke. *Stroke* 1993;24:1372–1375.
- 76 Toni D, Fiorelli M, Gentile M, et al: Progressing neurological deficit secondary to acute ischemic stroke: a study on predictability, pathogenesis, and prognosis. *Arch Neurol* 1995;52:670–675.
- 77 Finocchi C, Gandolfo C, Gasparetto B, Del Sette M, Croce R, Loeb C: Value of early variables as predictors of short-term outcome in patients with acute focal cerebral ischemia. *Ital J Neurol Sci* 1996;17:341–346.
- 78 Chamorro A, Vila N, Ascaso C, Elices E, Schonewille W, Blanc R: Blood pressure and functional recovery in acute ischemic stroke. *Stroke* 1998;29:1850–1853.
- 79 Ahmed N, Wahlgren G: High initial blood pressure after acute stroke is associated with poor functional outcome. *J Intern Med* 2001; 249:467–473.
- 80 Bhalla A, Wolfe CD, Rudd AG: The effect of 24 h blood pressure levels on early neurological recovery after stroke. *J Intern Med* 2001;250: 121–130.
- 81 Boreas AM, Lodder J, Kessels F, de Leeuw PW, Troost J: Prognostic value of blood pressure in acute stroke. *J Hum Hypertens* 2002;16:111–116.
- 82 Aslanyan S, Fazekas F, Weir CJ, Horner S, Lees KR: 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: 2420–2425.
- 83 Semplicini A, Maresca A, Boscolo G, et al: Hypertension in acute ischemic stroke: a compensatory mechanism or an additional damaging factor? *Arch Intern Med* 2003;163: 211–216.
- 84 Vlcek M, Schillinger M, Lang W, Lalouschek W, Bur A, Hirschl MM: Association between course of blood pressure within the first 24 h and functional recovery after acute ischemic stroke. *Ann Emerg Med* 2003;42:619–626.
- 85 Rodriguez-Garcia JL, Botia E, de La Sierra A, Villanueva MA, Gonzalez-Spinola J: Significance of elevated blood pressure and its management on the short-term outcome of patients with acute ischemic stroke. *Am J Hypertens* 2005;18:379–384.
- 86 Stead LG, Gilmore RM, Decker WW, Weaver AL, Brown RD Jr: Initial emergency department blood pressure as predictor of survival after acute ischemic stroke. *Neurology* 2005; 65:1179–1183.
- 87 Dunne JW, Chakera T, Kermode S: Cerebellar haemorrhage – diagnosis and treatment: a study of 75 consecutive cases. *Q J Med* 1987; 64:739–754.
- 88 Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G: Volume of intracerebral hemorrhage: a powerful and easy-to-use predictor of 30-day mortality. *Stroke* 1993;24:987–993.
- 89 Dandapani BK, Suzuki S, Kelley RE, Reyes-Iglesias Y, Duncan RC: Relation between blood pressure and outcome in intracerebral hemorrhage. *Stroke* 1995;26:21–24.
- 90 Qureshi AI, Safdar K, Weil J, et al: Predictors of early deterioration and mortality in black Americans with spontaneous intracerebral hemorrhage. *Stroke* 1995;26:1764–1767.
- 91 Fogelholm R, Avikainen S, Murros K: Prognostic value and determinants of first-day mean arterial pressure in spontaneous supratentorial intracerebral hemorrhage. *Stroke* 1997;28:1396–1400.
- 92 Terayama Y, Tanahashi N, Fukuuchi Y, Gotoh F: Prognostic value of admission blood pressure in patients with intracerebral hemorrhage. Keio Cooperative Stroke Study. *Stroke* 1997;28:1185–1188.
- 93 Leira R, Davalos A, Silva Y, et al: Stroke Project, Cerebrovascular Diseases Group of the Spanish Neurological Society. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. *Neurology* 2004;63:461–467.

Counterstatement

Editorial: ‘Pathophysiology of Brain Ischemia: Penumbral, Gene Expression, and Future Therapeutic Options’ (Eur Neur 2005;54:179–180)

The publication of the above-mentioned editorial was accompanied by an ‘Erratum’ of which the undersigned author of the editorial had not been informed. He had not been given the opportunity to comment on its content prior to its publication and therefore, a previous clarification of the issue was impossible.

Please note that Prof. Mathias Bähr has personally substantially reviewed the final manuscript of the editorial that explicitly states his co-authorship. Prof. Mathias Bähr knew about and agreed upon the publication of the manuscript.

Dr. Bernhard Schaller