REVIEW

Blood pressure in acute stroke

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Abstract

Elevated systolic blood pressure levels (≥160 mmHg) are a common complication of acute stroke, affecting up to 60% of patients, and providing an immediate management dilemma in the 40% of acute stroke patients on pre-existing antihypertensive therapy. There are theoretical reasons for both lowering blood pressure in the acute stroke situation, as well as leaving raised levels untreated. Furthermore, low systolic blood pressure levels (≤140 mmHg), though a less common problem affecting approximately 20% of patients, may also be associated with increased morbidity and mortality. However, limited data exists from randomised, placebo-controlled trials to inform as to the optimum management of acute stroke blood pressure. This review will consider the evidence for and against the therapeutic manipulation of acute stroke blood pressure, and discuss the information currently available from observational and therapeutic intervention trials, as well as consider the ongoing clinical trials in this area.

Keywords: cerebrovascular disease, blood pressure, hypertension, hypotension

Introduction

Stroke is the most common life-threatening neurological condition, newly affecting 110,000 patients per annum in the UK [1], the third most common cause of death and the most important single cause of severe adult disability [2,3]. Not surprisingly, stroke represents a significant cost to the National Health Service (NHS), consuming 4.4% of NHS expenditure with stroke patients occupying 13% of all NHS beds. Accordingly, the National Service Framework for Older People calls for the establishment of specialist stroke services supported by the implementation of the Royal College of Physicians National Clinical Guidelines for the management of common post-stroke problems [4].

Hypertension is a well recognized complication following acute stroke, the International Stroke Trial [5] and the Chinese Acute Stroke Trial [6] reporting 82% and 75% of patients, respectively, had systolic blood pressure (SBP) levels >140 mmHg within the first 48 hours following acute stroke. Indeed, these same trials identified that 28% and 25% of patients had markedly raised SBP levels >180 mmHg. Furthermore, 40% of acute stroke patients on hospital admission are already receiving antihypertensive therapy [7]. However, the management of hypertension post-stroke has remained a matter of some debate [8, 9].

This is reflected in surveys of clinical practice, e.g. the Stroke Association reported that 6% of physicians would start antihypertensive treatment immediately on admission, 21% would wait a few hours, though the rest would wait anything from a few days to a few weeks [10]. A similar lack of consensus exists in the United States, where the University Health Consortium Stroke Benchmarking Project reported that 57% of stroke patients received antihypertensive therapy following admission, of these 54.5% continued pre-admission drugs while 45.5% had therapy introduced de novo. Furthermore, there was significant variability in the thresholds used to intervene, 67% using SBP ≥180 mmHg and 33% using values <180 mmHg [11].

Hypotension is a less common finding; nonetheless 18% of patients in the International Stroke Trial [5] and 25% in the Chinese Acute Stroke Trial [6] had SBP ≤140 mmHg within 48 hours of stroke onset. As will be discussed, hypotension may not be a benign phenomenon, but again there is a lack of consensus regarding its management.

Therefore, this review will discuss the management of BP in the acute stroke situation, in particular highlighting the potential advantages and disadvantages of acute BP manipulation. Furthermore, current evidence from acute intervention and observational studies will be considered, as well as highlighting ongoing research to address this important clinical question.
Acute stroke blood pressure changes: should we intervene?

There are theoretical reasons against the acute treatment of hypertension immediately post-stroke. Firstly, the natural history is for a spontaneous reduction in BP levels over a period of four to ten days [12–14, 15]. Secondly, there are well-documented impairments in cerebrovascular reactivity following acute stroke [16–18], and we have shown that dynamic, but not static, cerebrovascular autoregulation is impaired immediately post-stroke [19]. Thus, cerebral blood flow becomes dependent on systemic BP levels, and any reduction in the latter may have potential adverse consequences for ischemic penumbral viability. Thirdly, there is mounting evidence for impaired autonomic nervous system control of the cardiovascular system following acute stroke [20], which further adversely affects the physiological responses to systemic BP changes. In particular, there is impairment of both cardiac and vasomotor arms of the baroreceptor reflex [21], as evidenced by impaired responses to orthostasis [22] and lower body negative pressure [23]. Finally, data from the International Stroke Trial (IST) suggests that increasing SBP levels (assessed within 48 hours of stroke onset) of over 150 mmHg are independently associated with the risk of early (<2 week) recurrent ischemic stroke; every 10 mmHg rise being associated with a 4.2% increase in early recurrence [24]. Furthermore, sustained increases in BP may be harmful by increasing cerebral edema and the likelihood of hemorrhagic transformation of the infarct [25], though interestingly no association between baseline SBP and symptomatic intracranial hemorrhage was reported in the IST [24].

Observational studies

In keeping with the pathophysiological changes in BP and BP control following acute stroke, the data from a number of observational studies suggest that both high [26–35, 36, 37] and low [38] BP in the acute stroke period may be associated with a poor short-term prognosis (Table 2*). However, some studies have found no relationship between BP and short-term outcome [39, 40, 41], though Carlberg and colleagues [39] did report that hypertension was associated with poor prognosis in those patients with impaired conscious level. Previous studies have similarly demonstrated a relationship between high [42–50, 51, 52–53] and low [54–56] acute stroke BP and increased long-term mortality, though others have reported no relationship [57–70] (Table 3*).

Given the reported detrimental effects of both high and low BP levels post-ictus, it is interesting that the IST has recently reported a U-shaped relationship between casual SBP levels at randomisation (within 48 hours of acute ictus) and short-term (14 day mortality) and long-term (6 month death and dependency) outcomes, with the lowest risk corresponding to casual SBP of values of 150 mmHg [24].

However, there are other possible explanations for the discrepancies between these results, which have been documented previously [36, 71]. These relate to stroke type, the effects of concomitant treatment, the small size of most studies, and whether the association between BP and outcome was assessed independently from other prognostic factors. Discrepancies may also relate to BP measurements: numerous observers, variable time of recording with respect to onset of ictus, retrospective documentation from patient records, and lack of data on how BP was recorded. The technique of non-invasive 24-hour BP monitoring reduces measurement variability and observer bias compared to casually recorded BP [72], and may overcome some of these methodological issues. Using this method, we found an odds ratio for outcome of death or dependency at 30 days post-ictus associated with each 10 mmHg increase in 24-hour SBP recorded within 24 hours of symptom onset of 1.88 (95% confidence intervals: 1.27–2.78), with no evidence of a J-shaped relationship [36]. Bhalla and colleagues [27] also utilised 24-hour BP monitoring techniques, reporting an odds ratio for outcome of functional recovery at 7 days associated with each 10 mmHg increase in admission 24-hour SBP of 0.79 (0.60–0.99). It is not just short-term outcome that is influenced by 24-hour BP levels recorded shortly after stroke, it has also been shown that 24-hour SBP levels >160 mmHg recorded within 72 hours of ischemic stroke were independently associated with a significantly increased hazards ratio of 2.41 (1.24–4.67) for death over a median follow-up period of 3 years compared to a reference value of <140 mmHg [51].

However, it would be impractical to wait more than 24 hours for the results of 24-hour BP monitoring to inform the acute management of post-stroke hypertension. Therefore, it is encouraging that important prognostic information can also be obtained from a simple 10-minute period of non-invasive beat-to-beat BP monitoring. Using this methodology, it has been shown that not only BP levels but also BP variability, as assessed from the standard deviation, were significantly higher in those patients dead or dependent at 30 days. The odds ratio for a poor outcome was 1.38 (1.1–1.9) for every 10 mmHg increase in mean arterial BP, and 1.32 (1.1–1.7) for every 1 mmHg increase in mean arterial BP variability. Furthermore, by dividing the patients into BP quartiles and further splitting them into high and low BP variability, those with high diastolic and mean arterial BP variability were at significantly greater risk of poor outcome, whatever the BP range [73].

Intervention studies

The secondary prevention of recurrent cerebrovascular events (Figure 1) and major cardiovascular events (Figure 2) by antihypertensive therapy in both hypertensive and normotensive stroke survivors is increasingly established. However, until recently, the therapeutic management of BP in the acute stroke period has largely been based on anecdotal reports in the medical literature, which have highlighted the potential benefits of pressor agents [74–76] and the potential adverse effects of depressor therapy [77, 78]. Of course, the reality is less simplistic as highlighted by a series of 43 patients studied within 72 hours of acute stroke. Olsen and...
colleagues [79] identified a subgroup of eight patients with critically low cerebral blood flow with abnormal penumbral vascular reactivity who benefited from vasopressor angiotensin therapy, but also a subgroup of 12 patients with penumbral hyperaemia who were at increased risk of oedema and haemorrhage.

Studies assessing the relative merits of hypotensive therapy have been largely uncontrolled [80]. However, the Blood Pressure in Acute Stroke Collaboration has recently reviewed the evidence for the therapeutic manipulation of acute stroke BP from randomised, placebo-controlled, intervention trials [81, 82]. This and other evidence (where it exists) will now be considered for the major antihypertensive drug classes, though there remains a lack of data for certain agents including centrally acting agents.

Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme inhibitors (ACEI) shift the lower limit of cerebrovascular autoregulation, and therefore can also improve regional cerebral blood flow at low perfusion pressures [83]. Captopril [84] and perindopril [85] have been studied in acute ischaemic stroke patients, and tend to reduce BP with respect to placebo. This was not associated with an increase in early or end of trial death or disability outcomes, though the studies were too small to accurately assess outcome events [82]. Furthermore, perindopril does not have adverse effects on cerebral blood flow, even in the presence of significant carotid artery disease [86].

Though the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [87] and Heart Outcomes Prevention Evaluation (HOPE) Study [88] have evaluated the use of perindopril (with and without indapamide) and ramipril, respectively, in the risk reduction of stroke in patients with a history of stroke, neither of these studies provides evidence to determine how acutely following stroke that ACEI therapy can be commenced safely. PROGRESS recruited patients a median of 8 months (interquartile range: 2–21 months) following stroke [87], and the HOPE Study does not

![Figure 1. Meta-analysis of the effects of antihypertensive therapy following stroke: fatal and non-fatal stroke recurrence.](http://ageing.oxfordjournals.org/)

![Figure 2. Meta-analysis of the effects of antihypertensive therapy following stroke: major cardiovascular events (non-fatal stroke, non-fatal myocardial infarction, vascular death).](http://ageing.oxfordjournals.org/)
clearly define the number of patients with a history of cerebrovascular disease nor does it state the time after stroke that therapy was started [88].

**Angiotensin II receptor blockers**

The Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS) trial has recently evaluated the use of an angiotensin-II inhibitor in hypertensive (>180/105 mmHg) acute ischaemic stroke patients, comparing acute (<72 hours) versus delayed (>7 days) intervention [89]. Preliminary data from 342 patients demonstrated a significant 47.5% reduction in all-cause, cerebral and cardiovascular mortality, though no effect on the combined primary outcome of death and disability at 3 months was seen [90].

**Beta-blockers**

Beta-blockers theoretically may be of benefit by limiting catecholamine-induced cardiac and neurological damage, and by reducing the metabolic demands of ischaemic brain. Barer and colleagues [91] compared propranolol (lipophilic) and atenolol (hydrophilic) with good and poor cerebral penetration, respectively, in a placebo-controlled trial of 302 patients within 48 hours of stroke. Significantly greater mean arterial BP falls from baseline were observed compared to placebo (2% fall) with both atenolol (9%) and propranolol (6%). However, both beta-blockers had a non-significant increase in mortality and decrease in neurological and functional outcome at 6 months compared to placebo, though functional differences were significant at 1 month.

Labetalol, a combined beta- and alpha-adrenergic antagonist, can be administered both intravenously and orally, producing minimal changes in heart rate and cardiac output without rebound hypertension on discontinuation and without producing tachyphylaxis [92]. It may therefore have beneficial properties in the treatment of post-stroke hypertension. Patel and colleagues [93] reported its bolus use at doses between 5 and 25 mg in a series of ten critically ill haemorrhagic stroke patients. Reductions of 6–19% in systolic and 3–26% in diastolic blood pressures were seen, without any reported adverse haemodynamic or mental state effects.

More recently, the use of labetalol has been reported in the context of the National Institutes of Neurological Disorders and Stroke (NINDS) thrombolysis trial with recombinant tissue plasminogen activator [94]. Nine per cent of patients in the placebo arm were hypertensive (≥185/110 mmHg) and received bolus intravenous labetalol therapy. The odds ratio for death at 3 months was significantly reduced compared to the 43 hypertensive patients in the placebo group who did not receive labetalol therapy (0.1, 0.1–0.7). However, the use of post-randomisation antihypertensive therapy in 65 patients in the treatment (rt-PA) group was associated with an increased risk of 3-month mortality (4.2, 2.0–9.0). Of course, the non-randomised use of antihypertensive therapy in the NINDS trial make these data very difficult to interpret.

**Calcium channel antagonists**

Calcium channel antagonists may have a cerebroprotective effect by limiting post-ischaemic intracellular calcium influx. In addition, these agents may be beneficial in acute stroke because of a preferential vasodilatory action on cerebral blood vessels with an increase in cerebral blood flow [95]. These agents have been assessed both intravenously and orally in acute ischaemic stroke, and these trials have been considered in recent extensive reviews [81, 82, 96]. The review by Horn and colleagues [96] identified 47 trials assessing calcium channel antagonist use in acute ischaemic stroke, including 29 trials of 7665 patients in their systematic review. No effect of calcium antagonists on poor outcome (relative risk: 1.04, 0.98–1.09) or death (1.07, 0.98–1.17) at the end of follow-up was reported. The Blood Pressure in Acute Stroke Collaboration included eleven trials of calcium channel antagonists. Oral use was associated with a non-significantly increased combined end-of-trial case fatality and disability (Odds ratio: 1.28, 0.98–1.67) [82]. More recently, Ahmed and colleagues have reported an association between diastolic BP reduction and neurological worsening following high dose intravenous nimodipine administration in the Intravenous Nimodipine West European Stroke Trial (INWEST) [97].

**Nitrates**

Nitric oxide is also a potent cerebral vasodilator and may beneficially improve regional cerebral blood flow [98]. Furthermore, it has antiplatelet actions, antileucocyte actions [99], and antagonises the N-methyl-D-aspartate receptor [100]. These actions may potentially reverse a number of detrimental pathophysiological changes associated with acute stroke. A small study with transdermal nitrate has demonstrated a significant BP reduction compared to placebo in acute ischaemic stroke patients [82, 101]. However, the clinical usefulness of nitrate may be limited by tolerance and carotid steal syndrome.

**Thiazide diuretics**

Thiazide diuretics are of proven benefit in the primary [102] and secondary prevention [103] (Figure 1) of stroke, particularly when used in combination with an ACEI [87]. We have studied the acute use of bendrofluazide 2.5 mg daily in 41 ischaemic stroke patients in a placebo-controlled trial. Treatment was commenced within 96 hours and continued for 7 days. No significant effects were observed on either absolute BP level or BP variability compared to placebo, and therefore bendrofluazide is an unsuitable agent to use if BP reduction is required in the immediate post-stroke phase [104].

**Pressor therapy**

Post-stroke hypotension, though a less common clinical problem [5, 6], may also be associated with adverse outcomes: a 17.9% increase in early (<2 week) death for every 10 mmHg SBP fall below 150 mmHg and an excess of coronary heart disease death [24]. Though induced hypertension is a standard treatment for cerebral ischaemia in patients with vasospasm after subarachnoid haemorrhage [105], there are few experimental data and little human data to support this practice following acute ischaemic stroke. However, up to 12% of patients were reported to receive inotropic support in...
a European survey of acute physiological stroke management [106]. Increasing BP levels in patients with low systemic BP values could reduce focal cerebral injury by increasing intraluminal hydrostatic pressure, opening collateral channels and improving perfusion to penumbral ischaemic tissue [107, 108].

Hypervolaemia has been used in isolation [109] and with dobutamine [110], and is associated with neurological recovery in stroke patients with middle cerebral artery occlusion, albeit in a series of 5 and 1 patients, respectively. Inotropes have also been used in larger patient series [111, 112]. Rordorf and colleagues [111] infused phenylephrine in a series of 13 acute stroke patients at a rate of 40–300 µg/min to maintain a 20% increase from baseline systolic BP over a period of at least 60 minutes. The infusion was maintained for a period of up to 6 days in responders, of whom there were 7, who maintained an improvement in their National Institutes of Health Stroke Scale score of ≥2 until discharge. Norepinephrine infusion has also been used to induce hypertension in a group of 19 acute complete or sub-total middle cerebral artery territory stroke patients, and is associated with enhanced cerebral perfusion without detrimental increases in intracranial pressure [112]. Saxena and colleagues [82] have assessed the use of diaspirin cross-linked haemoglobin (DCLHb) compared to placebo to increase BP for 72 hours in 85 patients recruited within 18 hours of ischaemic stroke. However, this was associated with a significant increase in the odds of combined death and disability (4.4, 1.81–10.85). Nonetheless, evidence in support of hypervolaemic and inotropic therapy is largely anecdotal, and further controlled trials are required.

**Current consensus**

Current guidelines recommend therapeutic intervention for only a few specific indications [113–115] (Table 1), and make no recommendation with respect to the management of acute stroke hypotension. However, these guidelines predate the current Cochrane Collaboration Stroke Reviews, which conclude that it remains unclear whether high BP should, or should not, be altered therapeutically during the acute phase of stroke [81, 82]. Nonetheless, post-stroke BP changes are a common clinical problem, with up to 80% of patients exhibiting acute stroke hypertension [116]. A recent questionnaire sent to United Kingdom Stroke Physicians highlighted the need for trials to address this issue, 83% responding positively [117]. Indeed, acute BP manipulation is the subject of at least three ongoing trials.

**Table 1. Indications for acute stroke blood pressure reduction: current guidelines [113–115]**

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<tr>
<th>Hypertensive encephalopathy</th>
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<tr>
<td>Cardiac/vascular urgencies</td>
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<tr>
<td>-Aortic dissection</td>
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<td>-Acute myocardial infarction</td>
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<td>-Unstable angina</td>
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<td>-Severe left ventricular failure</td>
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<td>BP &gt;200/120 mmHg in association with intracerebral haemorrhage</td>
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**Ongoing trials**

The Control of Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) Trial is a randomised, double-blind, placebo-controlled, step-therapy trial. At present, the pilot phase is assessing the management of non-dysphagic, hypertensive patients recruited within 24 hours of acute ischaemic stroke onset, and randomised to low-dose ACEI or matched placebo. BP levels are reviewed at 1 week and therapy increased to high-dose ACEI if target BP has not been achieved. Future pilot phases will assess depressor therapy using linsopril and labetalol compared to placebo in both dysphagic (given sublingually or intravenously, respectively) and non-dysphagic (given orally) hypertensive (SBP ≥160 mmHg) ischaemic and haemorrhagic stroke patients recruited within 24 hours of onset. Dose titrations will be made at 4 and 8 hours post-randomisation with the aim of achieving target BP [150 mmHg (range 145–155 mmHg) or a 15 mmHg reduction from baseline], with treatment continued until 2 weeks following stroke. Furthermore, hypertensive (SBP ≤140 mmHg) patients recruited within 12 hours of non-haemorrhagic stroke will receive intravenous phenylephrine infusion to achieve target SBP [150 mmHg (range 145–155 mmHg) or a 15 mmHg rise from baseline]. Pressor treatment will be continued for a 24-hour period only. The primary outcome measure for the definitive CHHIPS Trials will be death and dependency at 2 weeks post-stroke, and secondary neurological, disability and health-related quality of life outcomes will be collected at 2 weeks and 6 months [118] (www.le.ac.uk/medther/).

The Efficacy of Nitric Oxide in Stroke (ENOS) Trial is a prospective, multicentre, randomised, parallel-group, double-blind, placebo-controlled trial designed to test the safety and efficacy of nitric oxide, given as transdermal glyceryl trinitrate, and of continuing or stopping antihypertensive medication.

Up to 5000 patients will be recruited within 48 hours of acute ischaemic and haemorrhagic stroke onset, and treated for 7 days. The primary outcome measure is death and dependency at 3 months. Early secondary outcomes will be assessed at 7 days, and include recurrent stroke, BP changes, adverse events, and venothromboembolic complications. Late secondary outcome measures will be recorded at 3 months, and include Barthel Index, EuroQol, cognition, and use of functional aids [119] (www.nottingham.ac.uk/stroke-medicine/).

However, at least 40% of acute stroke patients are already taking antihypertensive therapy on hospital admission [7], and it also remains uncertain if pre-existing therapy should be continued or stopped. The Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) will establish the efficacy and safety of BP manipulation in the acute stroke period by the continuation or stopping of pre-existing therapy. This United Kingdom, multicentre, prospective, randomised, open, blinded-endpoint study, stratified by age (<75 versus ≥75 years), will assess whether existing antihypertensive therapy should be continued or discontinued within the first 24 hours following ischaemic and haemorrhagic stroke onset. It is anticipated that 8400 patients will be screened to provide a study population of 2900 patients. The study has a 90% power at the 5% significance level to detect...
a relative reduction of 10% in death and dependency at 2 weeks between the continuation and discontinuation groups. Secondary outcomes will include neurological, disability, and quality of life outcomes at 2 weeks and 6 months, as well as 6-month mortality [120] (www.le.ac.uk/medther/).

Summary

In conclusion, how to manage BP in the acute stroke situation is a common clinical problem, though current guidelines recommend intervention for only a few specific instances. Nonetheless, there are theoretical arguments for and against the treatment of acute stroke hypertension and hypotension. Moreover, there is limited evidence from randomised, controlled clinical trials to support intervention. However, there are now three major ongoing clinical trials to address these important clinical questions for both newly hypertensive (CHHIPS, ENOS) and hypotensive (CHHIPS) patients, as well as those on pre-existing antihypertensive therapy (COSSACS, ENOS).

Key points

- Blood pressure changes, particularly hypertension, are common post-stroke.
- Post-stroke hypertension and hypotension may be associated with increased morbidity and mortality.
- The benefits and risks of blood pressure manipulation following acute stroke are not clearly established.
- Ongoing trials will address these issues for stroke patients on pre-existing antihypertensive therapy (COSSACS, ENOS) and for both hypertensive (CHHIPS) and hypotensive (CHHIPS, ENOS) patients.

References

PLEASE NOTE: The very long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available on our website: http://www.ageing.oupjournals.org/


*Available online at www.ageing.oupjournals.org

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