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REVIEW ARTICLE

Antihypertensive therapy in acute ischemic stroke: where do we stand?

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Abstract

Despite the proven benefits of strict blood pressure (BP) control on primary and secondary prevention of stroke, management of acute hypertensive response in the early post-stroke period is surrounded by substantial controversy. Observational studies showed that raised BP on ischemic stroke onset is prognostically associated with excess risk for early adverse events and mortality. By contrast, randomized controlled trials and recent meta-analyses showed that although antihypertensive therapy effectively controls elevated BP in the acute stage of ischemic stroke, this BP-lowering effect is not translated into improvement in the risk of death or dependency. On this basis, acute and aggressive BP responses within 24 h of stroke onset should be avoided and antihypertensive therapy is recommended only for patients presenting with acute ischemic stroke and BP > 220/120 mmHg or those with BP > 185/110 mmHg who are eligible for therapy with intravenous tissue plasminogen activator. By contrast, recent clinical trials showed that intensive BP lowering to levels < 140 mmHg for systolic BP is safe and lowers the risk of hematoma expansion in patients with acute intra-cerebral hemorrhage and this BP target is recommended by current international guidelines. Herein, we provide an overview of randomized trials and recent meta-analyses on the management of hypertension during the acute stage of ischemic stroke. We discuss several areas of uncertainty and conclude with perspectives for future research.

Introduction

Elevated blood pressure (BP) is very common in the acute phase of ischemic stroke, affecting up to three-quarters of patients [1, 2]. The pathogenesis of this acute hypertensive response is complex and not yet fully understood. On one hand, early BP elevation may be attributable to abnormal neuro-endocrine response to physiological stress or may simply reflect pre-existing undiagnosed or inadequately controlled hypertension [3–6]. On the other hand, however, a number of stroke-specific factors (i.e., intracranial hypertension, cerebral auto-regulatory impairment, collateral insufficiency, clot burden) are proposed as mediators of acute hypertensive response in the early post-stroke period [3–6]. Management of hypertension in the acute stage of stroke is surrounded by controversy. Whereas several observational studies have provided a clear prognostic association of raised BP with excess mortality and poor functional outcome [7–11], randomized trials [4, 6, 12, 13] and recent meta-analyses [14] failed to prove that controlling high BP in acute phase of stroke is beneficial.

In this article, we provide an overview of clinical trial and meta-analytic evidence on the safety and efficacy of BP lowering in the acute stage of ischemic stroke. We explore several areas of uncertainty in management of hypertension in this particular setting and conclude with perspectives for future research.

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Table 1 Major randomized controlled trials evaluating the safety and efficacy of antihypertensive therapy in acute phase of ischemic stroke

Trial	*n*	Type of stroke	Design	Age (yrs)	Baseline BP (mmHg)	Intervention	Timing of intervention	Follow-up	Overall effect	Results
IMWEST (2000) [15]	295	Ischemic	Double-blind	72	A: 160/89 C: 160/91	Nimodipine IV 1 or 2 mg/h vs. placebo for 5 days, followed by oral therapy for another 16 days	Within 24 h post-stroke	21 days	Negative	DBP lowering ≥ 20% was associated with higher risk for death or dependency at day 21 (OR: 10.16; 95% CI: 1.02–100.74)
ACCESS (2003) [16]	339	Ischemic	Double-blind	68	A: 188/99 C: 190/99	Oral candesartan 4 mg/day (titrated up to 16 mg/day) vs. placebo for 7 days	Within 24 h post-stroke	12 months	Positive	Candesartan lowered by 52.5% the risk of vascular events and death during follow-up (OR: 0.475; 95% CI: 0.252–0.895)
CHIPPS (2009) [17]	179	Ischemic or hemorrhagic	Double-blind	74	A: 182/95 C: 181/96	Oral/sublingual lisinopril (5 mg/day) vs. oral/IV labetalol (50 mg/day) vs. placebo	24–36 h post-stroke	3 months	Neutral	No between-group difference in incidence of all-cause death or dependency at day 15 (RR: 1.03; 95% CI: 0.80–1.33) in the overall study cohort, as well as in subgroup of participants with ischemic stroke
PRoFESS (2009) [18]	1360	Ischemic	Double-blind	66	A: 146/84 C: 147/84	Oral telmisartan (80 mg/day) vs. placebo	72 h post-stroke	3 months	Neutral	Telmisartan was not superior to placebo in lowering the risk of death or dependency at day 30 (OR: 1.03; 95% CI: 0.84–1.26)
COSSACS (2010) [19]	763	Ischemic or hemorrhagic	Open-label, blinded end-point	74	150/81	Continue vs. stop of pre-existing antihypertensive therapy	Within 48 h post-stroke	6 months	Neutral	Continuation of antihypertensive therapy did not improve the primary outcome of death or dependency at day 15 (RR: 0.86; 95% CI: 0.65–1.14)
SCAST (2011) [20]	2029	Ischemic or hemorrhagic	Double-blind	71	A: 171/90 C: 172/91	Candesartan (4–16 mg/day) vs. placebo	Within 30 h post-stroke	6 months	Neutral	Candesartan did not lower the risk of vascular events and mortality during 6 months of follow-up relative to placebo (HR: 1.09; 95% CI: 0.84–1.41). Similar effects in the ischemic stroke subgroup
CATIS (2014) [13]	4071	Ischemic	Single-blind	62	A: 167/97 C: 167/96	Receive vs. discontinue antihypertensive therapy	Within 24 h post-stroke	3 months	Neutral	Active therapy did not improve the primary outcome of death or major disability at day 14 or hospital discharge relative to no antihypertensive treatment (OR: 1.00; 95% CI: 0.88–1.14)
ENOS (2015) [12]	4011	Ischemic or hemorrhagic	Partial 2 × 2 factorial	70	A: 167/90 C: 167/89	Glyceril trinitrate dermal patch (5 mg/day) vs. no patch AND continue vs. withdrawal of pre-existing antihypertensive therapy	Within 48 h of stroke onset	3 months	Neutral	Both interventions were unable to modify the primary functional outcome at day 90 in patients with either ischemic or hemorrhagic stroke
VENTURE (2015) [22]	393	Ischemic	Open-label, blinded end-point	65	A: 162/90 C: 163/92	Valsartan (80 mg/day) vs. no treatment	Within 48 h of stroke onset	3 months	Neutral	No between-group difference in the primary outcome of death or dependency at day 90 (OR: 1.11; 95% CI: 0.67–1.79)

A active, *ACCESS* Acute Candesartan Cilexetil Therapy in Stroke Survivors, *BP* blood pressure, *C* control; *CATIS* China Antihypertensive Trial in Acute Ischemic Stroke, *CHIPPS* Controlling Hypertension and Hypotension Immediately Poststroke, *COSSACS* Continue or Stop Post-Stroke Antihypertensives Collaborative Study, *CI* confidence interval, *DBP* diastolic blood pressure, *HR* hazard ratio, *IV* intravenous, *INWEST* Intravenous Nimodipine West European Stroke Trial, *OR* odds ratio, *PRoFESS* The Prevention Regimen for Effectively Avoiding Second Stroke, *RR* relative risk, SCAST the angiotensin-receptor blocker candesartan for treatment of acute stroke, *VENTURE* Valsartan Efficacy on Modest Blood Pressure Reduction in Acute Ischemic Stroke

Clinical trial evidence

The effect of BP lowering in the acute phase of ischemic stroke on the risk for early adverse events and mortality has been evaluated in a number of randomized trials, which are summarized in Table 1 and discussed in detail below.

In the Intravenous Nimodipine West European Stroke Trial (IMWEST) [15], 295 patients with acute ischemic stroke were randomized to intravenous nimodipine 1 or 2 mg/h or placebo for 5 days, followed by oral nimodipine (30 mg QID) or placebo for another 16 days. Nimodipine therapy was associated with worsening neurological symptoms during the first few days of stroke onset. Compared with placebo, patients in the high-dose nimodipine group with ≥ 20% drop in diastolic BP (DBP) had higher risk for death or dependency (defined as Barthel index < 60) during the 3-week-long follow-up [odds ratio (OR): 10.16; 95% confidence interval (CI): 1.02–101.74)] [15]. By contrast, the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) trial was prematurely terminated due to an imbalance in clinical outcomes favoring the administration of antihypertensive therapy in acute stage of ischemic stroke [16]. In this trial, 339 patients with ischemic stroke and BP ≥ 200/110 mmHg within 24 h of admission were randomized to candesartan (4–16 mg/day) or placebo for 7 days. Participants with uncontrolled hypertension on day 7—confirmed with 24-h BP monitoring—received higher doses of candesartan or add-on antihypertensive therapy, if necessary, targeting an office BP < 140/90 mmHg and were prospectively followed for 12 months [16]. Although BP levels during the acute phase of stroke were not different between the active treatment and placebo arms, candesartan lowered by 52.5% the risk of recurrent cerebrovascular or cardiovascular event and all-cause mortality during follow-up (OR: 0.475; 95% CI: 0.252–0.895) [16].

The Controlling Hypertension and Hypotension Immediately Post-Stroke (CHIPPS) trial randomized 179 patients with acute ischemic or hemorrhagic stroke and elevated systolic BP (SBP) > 160 mmHg within 36 h of symptom onset to double-blind therapy with lisinopril, labetalol or placebo for 14 days [17]. Compared with placebo, SBP during the first 24 h was by 10 mmHg lower in the combined active treatment group (between-group difference: 10 mmHg; 95% CI: 3–17 mmHg). This BP-lowering response was not associated with acute neurological deterioration at 72 h. Occurrence of the primary outcome of death or dependency at 2 weeks was not different between groups [relative risk (RR): 1.03; 95% CI: 0.80–1.33] [17]. Despite the small sample size and low statistical power, BP lowering with lisinopril or labetalol was accompanied by a marginally significant 60% reduction in the risk of all-cause mortality during a 3-month-long follow-up [hazard ratio (HR): 0.40; 95% CI: 0.20–1.00] [17].

The effect of BP lowering in acute phase of ischemic stroke was evaluated in a non-prespecified secondary analysis of 1360 patients participating in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial [18]. These patients were randomized to double-blind therapy with telmisartan (80 mg/day) or placebo within 72 h of stroke onset. Since PRoFESS was originally designed to explore the effect of telmisartan on secondary prevention of stroke, severity of stroke in patients enrolled in this secondary analysis was mild and baseline BP was lower than that of other trials (~147/84 mmHg) [18]. Compared with placebo, telmisartan exerted a more potent BP-lowering action during the first 7 days after randomization (between-group difference: −6.1/−3.2 mmHg, $P < 0.001$). However, death or dependency at day 30, which was the primary outcome of this analysis, did not differ between groups (OR: 1.03; 95% CI: 0.84–1.26) [18]. In addition, telmisartan was not superior to placebo in lowering the risk of cardiovascular death, recurrent stroke and myocardial infarction (MI) over a follow-up of 3 months (OR: 1.48; 95% CI: 0.78–2.79), despite the tighter BP control with telmisartan during follow-up [18].

In the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) [19], 763 patients with ischemic or hemorrhagic stroke were randomized to continue or halt pre-existing antihypertensive therapy for 2 weeks. Patient were enrolled within a median of 23.6 h after stroke onset (interquartile range: 17.9–34.8) and 16.0 h (interquartile range: 6.8–28.9) after the last dose of antihypertensive drug. The between-group difference in change of BP from baseline to 2 weeks was 13.0 mmHg (95% CI: 10–17 mmHg) for systolic and 8 mmHg (95% CI: 6–10 mmHg) for diastolic [19]. However, continuation of pre-existing antihypertensive therapy did not improve the primary outcome of death or dependency at 2 weeks (RR: 0.86; 95% CI: 0.65–1.14) [19]. Over a 6-month-long follow-up, the rates of adverse events, cardiovascular morbidity and all-cause mortality did not differ between treatment arms.

The Scandinavian Candesartan Acute Stroke Trial (SCAST) enrolled 2029 patients with acute stroke (ischemic 85%; hemorrhagic 14%) and baseline SBP ≥ 140 mmHg within 30 h of admission [20]. Study participants were randomized to candesartan (4–16 mg/day) or placebo from day 3 to day 7 of stroke onset. During the acute post-stroke period, BP levels were significantly lower in candesartan-treated than in placebo-treated participants (between-group difference on day 7: −4.9/−2.1 mmHg, $P < 0.001$). This BP-lowering effect of candesartan was not accompanied by a reduction in the risk of vascular death, MI or recurrent stroke over a 6-month-long follow-up (HR: 1.09; 95% CI: 0.84–1.41) [20]. Compared with placebo, candesartan was associated with a higher risk for poor functional outcome at

6 months, as assessed with the modified Raklin scale (OR: 1.17; 95% CI: 1.00–1.38) [20]. The absence of benefit was irrespective of the type of stroke (ischemic or hemorrhagic). In a secondary analysis incorporating long-term outcome data collected from national patient registries and cause-of-death registries for 1256 SCAST participants, candesartan therapy in acute stage of stroke was not associated with improvement in the composite outcome of vascular death, MI or recurrent stroke over a 3-year-long follow-up (HR: 0.87; 95% CI: 0.71–1.07) [21]. The impact of BP lowering during the acute phase of stroke on long-term clinical outcomes needs to be clarified in properly designed randomized trials.

In the China Antihypertensive Therapy in Acute Ischemic Stroke (CATIS) trial [13], 4071 patients with non-thrombolysed ischemic stroke within 48 h of onset and elevated SBP (140–220 mmHg) were randomized to receive BP-lowering therapy or discontinue their previous antihypertensive medications during hospitalization. The treatment algorithm in active treatment group prespecified a 10–25% reduction in SBP within 24-h after randomization, aiming to achieve a BP target < 140/90 mmHg on day 7 and maintain this level during hospitalization [13]. As expected, within the first 24 h, SBP was decreased by 21.8 mmHg in the active treatment group vs. 12.7 mmHg in controls. Compared with controls, SBP in actively treated participants was by 9.3 mmHg lower at day 7 and by 8.6 mmHg lower at day 14 after randomization. Incidence of death or major disability (defined as a modified Rankin scale ≥ 3) at 2 weeks or hospital discharge was identical in the active treatment and control groups (OR: 1.00; 95% CI: 0.88–1.14) [13]. Similarly, administration of antihypertensive therapy was not associated with reduced risk of death or major disability over a 3-month-long follow-up (OR: 0.99; 95% CI: 0.86–1.15) [13].

The Efficacy of Nitric Oxide in Stroke (ENOS) was a trial following a partial 2 × 2 factorial design, in which 4011 patients with acute stroke (ischemic 83%; hemorrhagic 16%) and elevated SBP (140–220 mmHg) were randomized to transdermal glyceryl trinitrate (5 mg/day) or no nitric oxide therapy for 7 days, initiated within 48 h of symptom onset [12]. A subgroup of 2097 participants previously treated with antihypertensive drugs were randomized to continue or halt their pre-existing BP-lowering therapy. Glyceryl trinitrate induced a significant BP-lowering action within 24 h after randomization (between-group difference: −7.0/−3.5 mmHg, $P < 0.001$) [12]. Compared with controls, BP in participants randomly allocated to continue pre-stroke antihypertensive therapy was lowered by 9.5/5.0 mmHg within 7 days of stroke onset. Compared with no treatment, transdermal glyceryl trinitrate did not improve the functional status assessed with the modified Rankin scale at day 90 (OR: 1.01; 95% CI: 0.91–1.13) [12]. Similarly, the functional outcome did not differ between participants randomized to continue vs. stop their pre-stroke antihypertensive therapy (OR: 1.05; 95% CI: 0.90–1.22). The cumulative incidence of serious adverse events or all-cause death over the 3-month-long follow-up was not affected by any of the above interventions [12].

In the Valsartan Efficacy on Modest Blood Pressure Reduction in acute ischemic stroke (VENTURE) trial [22], 393 patients with acute ischemic stroke and SBP ranging from 150 to 185 mmHg within 24 h of symptom onset were randomized to valsartan (80 mg/day) or no treatment for 7 days. Valsartan dose was modifiable aiming to achieve a 15% reduction in SBP levels or an SBP target of 145 mmHg during the first 7 days. Despite the comparable BP-lowering responses, early neurological deterioration at day 7 occurred more commonly in valsartan-treated participants than in controls (OR: 2.43; 95% CI: 1.25–4.73) [22]. Compared with no treatment, valsartan did not lower the risk of death or dependency (defined as a modified Rankin scale score of 3–6) at day 90 (OR: 1.11; 95% CI: 0.69–1.79). Over the 3-month-long follow-up, valsartan was not associated with improvement in the composite secondary outcome of non-fatal stroke, non-fatal MI or vascular death as compared with no treatment (OR: 1.41; 95% CI: 0.44–4.49) [22].

Meta-analytic evidence

In a 2014 meta-analysis of 17 randomized trials (incorporating data from 13,236 participants), Wang et al. showed that controlling high BP in acute stroke was associated with 34% higher risk of death within 30 days of stroke onset (RR: 1.34; 95% CI: 1.02–1.74) [23]. Early BP lowering had no benefit on a number of secondary endpoints, including early neurological deterioration, early and long-term dependency, as well as long-term risk for recurrent stroke, MI and all-cause death [23]. It has to be noted, however, that this meta-analysis combined trials regardless of the type of stroke and did not provide separate risk estimates for participants with ischemic stroke and intra-cerebral hemorrhage (ICH).

In an updated 2014 Cochrane meta-analysis of 26 randomized trials (involving 17,011 participants with acute stroke), Bath and Krishnan [14] showed that compared with placebo, active therapy induced significant reductions in BP levels within 24 h after randomization, regardless of the antihypertensive drug category. BP lowering in the acute phase of stroke was not associated with lower risk for death or dependency; this absence of benefit was consistent regardless of antihypertensive drug class (OR: 0.98; 95% CI: 0.92–1.05), or stroke type (OR: 0.98; 95% CI: 0.92–1.05) [14]. In addition, participants allocated to continue their pre-stroke antihypertensive therapy had worse

functional outcome and worse disability scores at the end of intervention relative to those randomized to temporal withdrawal of BP-lowering drugs (mean difference in Barthel Index: −3.2; 95% CI: −5.8, −0.6) [14].

A 2015 meta-analysis including 13 randomized trials with 12,703 participants, aimed to ascertain the effect of BP lowering within 72 h of ischemic stroke onset on the composite outcome of death or dependency at 3 months [24]. This meta-analysis excluded randomized trials on ICH and incorporated the results of the large-scale ENOS and VENTURE trials. Once again, compared with placebo, early BP lowering did not reduce the risk of death or dependency at 3 months (RR: 1.04; 95% CI: 0.96–1.13) [24]. Furthermore, early BP lowering exerted neutral effects on the risk for recurrent vascular events (RR: 0.90; 95% CI: 0.65–1.25), recurrent stroke (RR: 1.00; 95% CI: 0.54–1.84) and all-cause mortality (RR: 0.99; 95% CI: 0.83–1.17) [24].

A subsequent meta-analysis of 22 randomized trials (incorporating data from 11,088 participants) confirmed that administration of antihypertensive therapy in the acute phase of stroke effectively lowered BP relative to placebo, but this effect was not translated into improvement in functional and clinical outcomes [25]. Long-term dependency did not differ between actively treated participants and controls (OR: 1.013; 95% CI: 0.915–1.120). Similarly, active therapy was not superior to placebo in improving long-term survival (OR: 1.039; 95% CI: 0.883–1.222) [25].

Areas of uncertainty and future perspectives

Despite the fact that several randomized trials and meta-analyses were brought to light over the past few years, management of hypertension in the acute stage of ischemic stroke remains controversial. Currently, available guideline recommendations [26–28] mandate the delayed initiation of antihypertensive therapy in the early post-stroke period with the exception of (i) patients with markedly elevated BP (> 220/120 mmHg); (ii) those with BP > 200/110 mmHg and evidence of acute target-organ damage (i.e., acute kidney injury, aortic dissection, MI, hypertensive encephalopathy or acute pulmonary edema); (iii) patients with BP > 185/110 mmHg who are eligible for thrombolysis or BP > 180/105 mmHg during the 24-h period following reperfusion [26–28]. The American Heart Association/American Stroke Association (AHA/ASA) guidelines [26] recommend that acute and potent BP-lowering responses within 24 h of stroke onset should be avoided, but the exact levels at which BP should be targeted remain unspecified. The controversy is further magnified by the substantial heterogeneity across trials with respect to patient characteristics, stroke subtype and severity or timing of treatment initiation [29]. In the following section, we discuss areas of uncertainty that warrant further investigation in order to optimize the management of hypertension in acute ischemic stroke.

Subtype and severity of ischemic stroke

Ischemic stroke is a heterogeneous disease and pathogenesis of acute hypertensive response may vary considerably, depending on the type of stroke and severity of cerebral auto-regulatory impairment [1, 5]. For example, observational studies have associated lacunar infarction with significantly higher BP elevation in the acute phase as compared with other stroke subtypes [30–32]. The notion that stroke subtype is a confounding factor determining the efficacy of interventions altering BP in the acute phase of stroke is supported by a prespecified post-hoc analysis of the SCAST trial [33]. This analysis showed that magnitude of BP lowering in response to candesartan therapy during the 7 first days of stroke onset was greater in participants with lacunar infarction and partial anterior circulation. However, candesartan was associated with improvement in functional outcome at 6 months only in participants with large infracts (i.e., in those with total anterior circulation) (OR: 0.47; 95% CI: 0.22–1.01) [33]. No interaction between stroke subtype and treatment effect of candesartan on the combined outcome of non-fatal stroke, MI or vascular death was evident [33]. Since this post-hoc analysis can not provide direct cause-and-effect associations, the complex interaction between stroke subtype, BP-lowering response to therapy and risk for poor outcomes requires additional investigation in randomized trials.

Timing of treatment initiation

Following the concept of guideline recommendations [26–28], treatment algorithm in several trials prespecified the introduction of antihypertensive therapy in the sub-acute phase of ischemic stroke (i.e., 24–72 h after stroke onset). However, the aforementioned 2014 Cochrane meta-analysis provided some evidence supporting that initiation of antihypertensive therapy in the hyper-acute phase (within 6 h of stroke onset) may be beneficial in lowering the risk of death or dependency (OR: 0.86; 95% CI: 0.76–0.99) [14]. In a prespecified subgroup analysis of the large-scale ENOS trial [12], a shift in the distribution of modified Rankin scale was noted, depending the time to randomization. In the subgroup of participants randomized within < 6 h of stroke onset, transdermal glyceryl trinitrate was associated with 45% lower odds for poor functional outcome at day 90 relative to placebo (OR: 0.55; 95% CI: 0.36–0.84) [12]. The efficacy of early BP lowering in the hyper-acute phase of stroke is under investigation in the ongoing Rapid Intervention with Glyceryl Trinitrate in Hypertensive Stroke Trial-2 (RIGHT-2) [34]. This trial is planning to randomize

850 patients with suspected stroke and SBP ≥ 120 mmHg within 4 h of symptom onset to double-blind therapy with transdermal glyceryl trinitrate patch (5 mg/day) or sham patch for 4 days. The primary outcome is defined as the difference between groups in the incidence of death or dependency, assessed with the modified Rankin scale at day 90 after stroke onset [34].

By contrast, a recent secondary analysis of the CATIS trial showed that very early initiation of antihypertensive therapy was not associated with favorable outcome at 3 months [35]. Participants receiving treatment within < 12 h of stroke onset had significantly lower SBP reduction at day 1 after randomization in comparison with those receiving treatment within 12–23 and 24–48 h of stroke onset (SBP reductions: −8.7 vs. −9.5 vs. −9.6 mmHg, $P <$ 0.001). Participants who initiated antihypertensive therapy between 24 and 48 h of stroke onset had lower risk for death or major disability (OR: 0.73; 95% CI: 0.55–0.96), recurrent stroke (OR: 0.25; 95% CI: 0.08–0.74) and vascular events (OR: 0.41; 95% CI: 0.18–0.95) during a 3-month-long follow-up [35]. Trials randomizing patients with acute ischemic stroke into earlier vs. later initiation of antihypertensive therapy are warranted in order to elucidate this issue.

On-treatment BP change and outcomes

Although several observational studies have associated elevated baseline BP with poor short- and long-term outcome [36], acute BP changes in response to therapy may be also prognostically informative. In a 2009 meta-regression analysis of 37 randomized trials (involving 9008 participants), Geeganage et al. [37] showed the presence of a U-shaped or J-shaped association between on-treatment BP change and risk of death or dependency at the end of follow-up. Large decreases and any increase in on-treatment BP were both associated with worse outcome [37]. Although clinical outcome was not significantly improved at any degree of BP reduction, the lowest odds for early death occurred with BP lowering of 8.1 mmHg (OR: 0.87; 95% CI: 0.54–1.23); the lowest odds for death at trial completion occurred with BP lowering of 14.4 mmHg (OR: 0.96; 95% CI: 0.31–1.65); the lowest odds for combined death or dependency at the end of follow-up occurred with BP lowering of 14.6 mmHg (OR: 0.95; 95% CI: 0.11–1.72) [37]. A similar U-shaped association of treatment-induced change in BP over 48 h of stroke onset with the risk of early adverse events (including recurrent stroke, progression of stroke and symptomatic hypotension) was observed in a post-hoc analysis of the SCAST trial [38]. Compared with participants manifesting modest BP-lowering responses, those with large reductions in SBP (OR: 2.08; 95% CI: 1.19–3.65) or increase/no change in SBP (OR: 1.96; 95% CI: 1.13–3.38) had significantly higher risk for early adverse events [38]. Baseline BP, time to randomization, history of pre-existing hypertension, severity and type of stroke were independent predictors of BP-lowering response to antihypertensive therapy [38]. Identification of factors enabling the prediction of the BP-lowering response may facilitate the individualization of antihypertensive therapy in the acute phase of ischemic stroke.

BP variability and outcomes

Certain and unavoidable limitations of conventional clinic BP recordings, including BP response to hospital admission, observer bias, measurement variability and inaccuracy in detecting treatment-induced BP-lowering responses, suggest that 24-h BP monitoring may have a particular role in assessment and management of hypertension in acute ischemic stroke [4, 39]. Most importantly, BP in acute phase of stroke does not follow a steady pattern, but exhibits excessive short-term and day-to-day variability that may be not adequately captured with clinic BP recordings [1, 5]. A recent meta-analysis of observational studies showed that an increase of 9.1 mmHg in 24-h SBP and an increase of 2.3 mmHg in 24-h DBP assessed immediately after stroke onset were both associated with poor short-, mid- and long-term functional outcome [40]. In contrast, conventional clinic BP recorded on admission was of no prognostic significance [40]. In addition, prospective observational studies have shown that short-term and day-to-day BP variability can prognosticate the risk of dependency and poor functional outcome independently from conventional risk factors and average BP [41–44]. Whether antihypertensive therapy can control short-term BP variability and the association of treatment-induced reduction in BP variability with clinical outcomes requires properly designed trials using 24-h BP monitoring in acute phase of ischemic stroke.

Acute ICH

Acute BP lowering among patients with ICH is an early therapeutic intervention to lower the risk of hemorrhagic expansion. This benefit of early intensive BP lowering, however, may be counteracted by risks associated with additive deterioration of the already compromised cerebral blood flow resulting in peri-hematomal hypo-perfusion and ischemia [6]. An earlier post-hoc analysis of 801 patients participating in the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial showed that a reduction in BP of no more than 20% within 24 h of admission was independently associated with lower risk of death at 3 months after ICH

onset (OR: 0.453; 95% CI: 0.262–0.784) [45]. The risk–benefit ratio of intensive BP lowering in acute ICH was explored is subsequent randomized trials and meta-analysis providing evidence that compared with conservative management, early intensive BP lowering is associated with greater attenuation of hematoma growth at 24 h, without any significant increase in the incidence of mortal events or major disability at 3 months of follow-up [46, 47]. On this basis, the revised 2015 AHA/ASA guidelines recommend an acute reduction in SBP to 140 mmHg during the first 24 h of admission for patients presenting with acute ICH and SBP ranging from 150 to 220 mmHg [48]. For those with SBP > 220 mmHg, aggressive BP lowering with continuous intravenous infusion of antihypertensive drugs in the intensive care unit is recommended as a reasonable therapeutic approach.

Asymptomatic hemorrhagic transformation is a common complication occurring in patients presenting with acute ischemic stroke. Incidence, determinants and prognostic association of asymptomatic hemorrhagic transformation of infarction with poor functional outcome were evaluated in a secondary analysis of 1484 patients participating in the Tinzapararin in Acute Ischemic Stroke Trial (TAIST) [49]. Using a repeat computed tomography scan at day 10 of stroke onset, the incidence of asymptomatic hemorrhagic transformation was as high as 29.2%. Participants with total anterior circulation syndrome (OR: 11.5; 95% CI: 7.1–18.7) and partial anterior circulation syndrome (OR: 7.2; 95% CI: 4.5–11.4) had higher odds for asymptomatic hemorrhagic transformation as compared with lacunar stroke [49]. Asymptomatic hemorrhagic transformation was not associated with worse functional outcome at 3 and 6 months of follow-up [49]. In contrast, symptomatic hemorrhagic transformation is a harmful complication that mitigates any benefit of anticoagulant therapy on stroke recurrence [50].

Conclusion

Despite the established benefits of BP lowering and adequate hypertension control on primary and secondary prevention of stroke [51–53], there is no convincing evidence from recent randomized trials and meta-analyses that controlling high BP in the acute stage of ischemic stroke is beneficial in lowering the risk of early death or dependency and in improving long-term clinical outcomes. Acute and aggressive BP lowering during the first 24 h of ischemic stroke onset is harmful and should be avoided. Current international guidelines recommend the use of antihypertensive therapy only in patients presenting with acute ischemic stroke and BP > 220/120 mmHg or those patients with BP > 185/105 mmHg who are eligible for reperfusion therapy. However, the exact levels at which BP should be targeted during the first hours to days after stroke onset remains elusive. Additional research efforts are warranted in order to shed more light on several areas of uncertainty and develop prognostic tools that will enable the identification of patients who may benefit from early BP lowering in the acute post-stroke period.

Summary Table – Highlights

- Acute BP elevation is a common clinical manifestation after an ischemic stroke and raised BP is associated with excess risk for premature death and later death or dependency.
- Randomized trials and recent meta-analyses showed that BP-lowering in the acute phase of ischemic stroke is not associated with improvement in short- and mid-term death risk and functional outcome.
- Current guideline recommend that aggressive BP-lowering during the first 24 hours of ischemic stroke onset should be avoided with the exception of patients presenting with BP >220/120 mmHg or those with BP >185/110 mmHg who are eligible for intravenous thrombolytic therapy.
- For intra-cerebral hemorrhage, clinical-trial evidence and current guidelines recommend that immediate and intensive BP-lowering to levels <140 mmHg for systolic BP is safe and beneficial.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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