

Ambiguities in blood pressure management in acute ischaemic stroke

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ABSTRACT

Introduction: Blood pressure management in acute ischaemic stroke is crucial. Here we highlight uncertainties surrounding haemodynamic management in acute ischaemic stroke on the basis of current guidelines and the data available from recent studies. This review provides practical treatment options and suggestions for future research.

State of the art: The U-shaped relationship between baseline blood pressure value and patients' functional outcome or death is well established. Nonetheless, there is scant evidence for the benefits of early pharmacological intervention. Current guidelines differentiate blood pressure targets on the basis of implemented reperfusion treatment and allow blood pressure reduction in certain clinical situations. However, there is a substantial lack of evidence to guide management during acute stroke.

Clinical implications: Taking into account several aspects of blood pressure management can improve stroke care, although they are not included in current guidelines. To make an optimal decision as to whether to intervene regarding blood pressure, it is important to consider dehydration, recanalisation status, blood pressure variability, and autoregulation state as measured by novel imaging techniques.

Future directions: Further trials considering patient-specific factors with the use of continuous monitoring of blood pressure, as well as neurovascular imaging, are needed to resolve the current ambiguities.

Key words: blood pressure, ischaemic stroke, acute management, revascularisation

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Introduction

Stroke is the third or, according to the World Health Organisation, perhaps even the second leading cause of death, and the third leading cause of disability worldwide [1–3]. Population-based studies in high-income countries show a consistent pattern of an increasing incidence of stroke at age < 60 years over the last few decades, whereas the incidence has actually declined in older age groups. The absolute incidence, however, is increasing [4]. In 2017, the Polish National Study concerning acute ischaemic stroke epidemiology showed that the crude and the standardised prevalence was 189.95 and 130.43 per 100,000 inhabitants, respectively [5].

Hypertension is one of the most critical risk factors for ischaemic stroke. In a recent (2020) study from West Pomerania, the ischaemic stroke patients who died, compared to those who survived, had hypertension about twice as often (OR = 2.57 in the univariable model; OR = 1.85 in the adjusted model, respectively) [6]. If we consider gender, women suffered from hypertension more often than men (78.3% vs. 70.1%) [7].

The high prevalence of hypertension among stroke patients is also clear from data on antihypertensive drug usage in hospitals — they were administered in 79.9% of first-ever stroke patients and in 84.4% of recurrent stroke patients in Poland [8].

Major progress in stroke management has been made since reperfusion therapies were first introduced into clinical

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practice. Intravenous thrombolysis (IVT) was implemented in 1995 in several randomised clinical trials (RCTs) and has proved effective in preventing poor outcomes in eligible patients with acute ischaemic stroke (AIS) [9, 10]. However, according to clinical trials, the administration of alteplase has resulted in recanalisation from 10% to 50% of patients [11–13]. A novel reperfusion technique, endovascular thrombectomy (EVT), has turned out to be much more effective in patients with large vessel occlusion (LVO), with results even exceeding 70% reperfusion rates [14].

As a result, EVT has become the gold standard of care in AIS. Unfortunately, a meta-analysis of 1,287 patient outcomes revealed that only 46% of participants who went through EVT had achieved functional independence at 90 days after their stroke — despite high rates of recanalisation [14]. This relatively low percentage of patients reaching functional independence has prompted the search for other factors that could improve patients' clinical outcome.

As a result, blood pressure (BP) in AIS has attracted major interest. Hypertensive response is a common phenomenon seen in stroke patients. However, it remains unclear whether it is a harmful reaction with potentially negative effects or a protective mechanism aiming to maintain cerebral blood flow. Proper control of BP in AIS is critical to the safe introduction of either IVT or EVT. The widely used American Heart Association/American Stroke Association (AHA/ASA) guidelines on haemodynamic management in reperfusion therapies propose stringent upper BP thresholds. When these are exceeded, causal treatment is contraindicated [15]. In contrast to the 'fixed to the threshold' attitude, recent studies have introduced a more personalised approach. Choosing a strict BP target for all patients may not take sufficiently into account patient-specific factors affecting cerebral perfusion after stroke. Maintaining the same BP threshold can lead to frequent episodes of hypoperfusion and hyperperfusion in vulnerable ischaemic tissue.

Hence in BP management a certain balance is needed to achieve the optimal values in order to avoid the risk of injury with further ischaemia or reperfusion syndrome.

Thus, the aim of this study was to discuss the uncertainties surrounding haemodynamic management in AIS on the basis of the currently applied guidelines and data drawn from recent studies.

State of the art

Current guidelines propose active lowering of BP in AIS patients in two clinical situations [15]. Firstly, in patients with BP $\geq 185/110$ who are eligible for either IVT or EVT. In either case, it is recommended to maintain BP below the threshold of 180/105 mmHg after the procedures regardless of whether reperfusion was successful. There is a significant difference in the strength of the recommendation for each procedure (Class I for IVT and Class 2a/2b for EVT).

The second clinical situation in which the guidelines suggest active lowering of BP occurs in patients ineligible for reperfusion therapies with BP $\geq 220/120$ mmHg or with pre-existing comorbid conditions (e.g. preeclampsia, acute coronary event, aortic dissection, acute heart failure). Unlike the upper threshold, the lower threshold of BP is not defined. Importantly, the present recommendations on BP management in EVT are not based on evidence from randomised trials. In fact, they are largely extrapolated from IVT trials [10] as well as retrospective studies [16]. There is a notable lack of evidence-based proofs to guide BP management during AIS and revascularisation therapies.

Ambiguities

Whether to treat elevated BP in AIS has long been a matter of debate [17, 18]. Recent trials have brought new insights to this subject. ENCHANTED and RIGHT-2 were both large RCTs designed to assess the efficacy of BP reduction [19, 20]. ENCHANTED was an international randomised, open-label, blinded-endpoint trial of 2,227 patients with acute stroke. RIGHT-2 was a multicentre ambulance-based, randomised, sham-controlled, phase III trial with masked outcome assessment designed to assess the safety and efficacy of glyceryl trinitrate (GTN) in a hyperacute stroke population.

The two trials have provided high level evidence that aggressive reduction of BP in hyperacute ischaemic stroke does not improve the functional outcome. Both studies were performed in patients eligible for thrombolysis therapy. In the setting of IVT, it is unknown whether and when recanalisation occurs. A sudden drop in BP in the pre-reperfusion period may increase the ischaemic area and could be the reason for the negative results in the abovementioned studies. Besides, the differences in systolic blood pressure (SBP) between treatment and control groups in both trials were fairly small (5–6 mmHg), which is relevantly low and its impact on cerebral perfusion is debatable. Additionally, the inclusion criteria were broad, which may have affected the findings.

However, there are several aspects regarding BP management that were not specified in the guidelines that one may take into account when deciding whether or not to interfere with BP in AIS. We consider these in the following paragraphs.

Hypovolemia and dehydration

It is stated in the guidelines that both hypotension and hypovolemia should be adjusted while aiming to maintain systemic perfusion levels necessary to support organ function [15]. Hypovolemia may reduce cerebral perfusion and increase the infarct core in ischaemic stroke and perihematomal ischaemia in intracerebral haemorrhage. The post-hoc analysis of the PASS trial has proved low baseline SBP in patients with AIS to be associated with an increased risk of in-hospital mortality and complications, particularly heart failure, gastrointestinal bleeding, and sepsis [21]. Nevertheless, a clearly defined

cut-off for low BP in AIS patients is lacking. Dehydration is a common phenomenon in AIS and is independently associated with poor clinical outcomes [22, 23]. Managing high BP with the use of antihypertensives may lead to precipitous drops in BP. Billington et al. assessed the impact of dehydration on the haemodynamic effects of antihypertensive treatment and prognosis in the ENOS trial [24]. There were no differences in terms of neurological impairment or in rates of reported hypotension, hypertension or headache by day 7, and no differences in neurological status at three months in those randomised to GTN compared to no GTN, or in those randomised to stop vs continue their pre-stroke antihypertensives. Lowering BP was safe in dehydrated patients, and triggered no precipitous changes in BP, thus supporting hypertensive management in acute stroke patients with blood markers of dehydration. Whether rehydration of dehydrated acute stroke patients has the potential to improve clinical outcome requires further trials.

Autoregulation-guided management

Cerebral autoregulation is a protective mechanism to maintain cerebral blood flow (CBF) despite changes in cerebral perfusion pressure. In normotensive patients, in the case of mean arterial pressure (MAP) fluctuations between 70 and 150 mmHg, CBF remains constant through vasoconstriction and vasodilation. Ischaemic symptoms in the central nervous system of a normotensive person start on average when the MAP at the level of the circle of Willis is 40–50 mmHg in a vertical position, and 45–55 mmHg in a supine position [25].

In patients with chronic hypertension, MAP values of autoregulation are higher, making these patients susceptible to hypoperfusion during hypotensive episodes [26]. Exceeding the specified ranges of MAP leads to a risk of harm due to uncontrolled changes in CBF. The existence of cerebral autoregulation in acute stroke plays a crucial role in the maintenance of a stable blood flow in the ischaemic penumbra and in the avoidance of excessive hyperperfusion [26, 27].

Therefore, potential fluctuations in autoregulatory compliance should be considered in the management of BP in the acute period following stroke. There is a lack of consistency across different studies, and different measurement modalities have been proposed for the assessment of cerebral autoregulation, such as near-infrared spectroscopy (NIRS) and transcranial Doppler ultrasounds (TCD).

Petersen et al. performed a single-centre, prospective cohort study in which the autoregulatory function was measured by interrogating changes in NIRS-derived oxygenation in response to changes in MAP [28]. The percentage of time when MAP exceeded the upper limit of autoregulation, or decreased below the lower limit of autoregulation, was calculated for every patient. Time above fixed systolic BP thresholds was computed in a similar fashion. Every 10% increase in time spent above the upper limit of autoregulation was associated with a 1.9-fold increase in the odds of shifting towards a worse

outcome on the modified Rankin Scale (mRS) at 90 days. Likewise, patients with haemorrhagic transformation of AIS spent more time above the upper limit of autoregulation. The authors proved that exceeding individual and flexible thresholds of autoregulation is associated with haemorrhagic transformation and overall worse functional outcome, even after adjusting for important prognostic covariates in stroke. They did not find this association when applying a fixed BP threshold, even when stratifying by reperfusion status [28].

TCD in AIS can provide information on cerebral vascular recanalisation, CBF status, and fluctuations in intracranial pressure, by measuring the blood flow velocity of the major intracranial arteries. Adding continuous BP measurement offers a method with a high temporal resolution feasible for bedside evaluation of cerebral autoregulation. TCD is widely used in stroke units at the bedside, and hence its use in BP management is easy to implement in clinical practice. Chen et al. performed a prospective trial including 95 AIS patients who were randomly divided into a TCD-guided group (TCB) and a non-TCD-guided group (NBC) [29]. They were monitored by TCD for 72 h after EVT. In the TCB group, BP and intracranial pressure were controlled under TCD monitoring using peak systolic velocity and pulsatility index target values of the middle cerebral artery (MCA). The management was performed according to a BP-lowering scheme, a BP-raising scheme, and an intracranial pressure-lowering scheme. The NBC were controlled according to the guidelines. The incidence rates of early neurological deterioration (END) and 3-month mortality in the TCB group were lower than those in the NBC group when TCD parameters were abnormal.

According to this study, when TCD show blood flow deceleration, BP should be elevated under the guidance of TCD monitoring. When TCD show an augmentation of intracranial pressure, the process of decreasing intracranial pressure should be guided by TCD monitoring. The authors hypothesised that the precise control of BP according to individual CBF parameters under TCD monitoring will change cerebral perfusion, reduce the risk of END, and improve prognoses and outcomes. An approach featuring autoregulation-based BP management seems reasonable, although further randomised trials are required.

Type of reperfusion therapy

Several trials have proved the U-shaped relationship between BP and outcome in AIS, with extreme values of BP having prognostic significance for disability and death [30, 31]. The recent post-hoc analysis of the MR CLEAN trial identified a U-shaped relationship between baseline SBP and good functional outcomes, with a nadir at 120 mmHg and a 21% increase in the relative risk of haemorrhage for every 10 mmHg above this value [32]. Nonetheless, clinical situations with patients ineligible for reperfusion therapies, those who received IVT, or both IVT and EVT, are entirely different and should be considered individually.

Although reperfusion therapies are nowadays widely available, there are still patients who are ineligible for either IVT or EVT, most frequently because of exceeding the therapeutic time window. Recent trials have lengthened the time for endovascular treatment up to 16 or even 24 hours [33, 34]. However, the prerequisite for applying EVT in this longer window is the use of imaging techniques which are not readily accessible, leading to the exclusion of some patients. The most recent guidelines recommend SBP to be maintained at a level of < 220 mmHg in the absence of IVT/EVT and < 180 mmHg after IVT/EVT, further highlighting that the usefulness of induced hypertension in patients with acute ischaemic stroke is not well established [15]. The results concerning permissive hypertension are divergent.

Bang et al. presented the effects of multicentre RCT in which for patients with noncardioembolic AIS ineligible for revascularisation therapy, therapeutic-induced hypertension was safe and increased the probability of early neurological improvement and long term independence (class III evidence) [35]. In this study, phenylephrine was administered intravenously to increase the SBP up to 200 mmHg. More patients in the intervention group experienced asymptomatic haemorrhagic transformation on follow-up MRI than in the control group. Interestingly, the effect of induced hypertension was also observed both in patients with large and small artery occlusions. The authors suggested a therapeutic SBP threshold of 180 mmHg in order to achieve beneficial effects. They also implied that the higher response than in former studies might have been the result of a higher therapeutic BP threshold than previously applied.

For instance, in Nasi et al.'s randomised single-centre controlled trial, patients without reperfusion therapies were divided into three groups: low (140–160 mmHg, median 153), medium (161–180, median 163 mmHg), and high (181–200 mmHg, median 178 mmHg) BP thresholds [36]. There was no difference in outcome among the three groups, but the greatest frequency of symptomatic intracerebral haemorrhage (sICH) was found in patients allocated to the higher range target. In logistic regression analysis, the probability of good outcome at day 90 was greater in the medium group compared to the high group (OR = 2.8). Perhaps the use of specific drugs is of more importance than previously thought (in the first trial, phenylephrine was the only drug, while in the second study different drugs, including oral and intravenous, were used). Additionally, the BP target should be more strictly respected (in Nasi et al.'s study in the high BP threshold group, the median BP was only 178 mmHg). In order to sustain adequate brain perfusion pressure, permissive hypertension may be beneficial in nonrecanalised patients. Individual differences in patient-specific factors may influence systemic and cerebral haemodynamics in the response to cerebral hypoperfusion and therapeutic-induced hypertension. Further RCTs assessing the safety and efficacy of permissive hypertension are required.

In the case of patients after recanalisation therapies, high BP appears to be detrimental and should probably be avoided [37–39]. Previous studies have displayed high BP after IVT to be linearly associated with haemorrhagic complications and worse outcomes [40–42]. Therefore, maintaining BP < 185/110 mmHg before IV rt-PA administration and < 180/105 mmHg for the first 24 hours after IVT appear to be valid. Special caution should be exercised in the use of antihypertensives and sudden BP declines after IVT. In the analysis of the NINDS trial, patients treated with antihypertensives had more abrupt BP drops and worse clinical outcomes at three months compared to hypertensive patients who were not treated with pharmacological drugs [40].

For patients undergoing EVT treatment, there is considerably less data concerning BP management. We know exactly when the vessel is recanalised in EVT. However, we do not know when or whether it comes to reperfusion in IVT. For that reason, the same BP targets for each reperfusion therapy might not apply. Uncertainties concern accurate BP management before, during, and after the EVT procedure with regard to the recanalisation effect (successive recanalisation TICI 2b/3 or \leq 2a).

Post-hoc analysis of the MR CLEAN study showed that baseline BP does not affect the safety of EVT in patients with proximal LVO [32]. Apart from the ESCAPE trial, all pivotal trials introducing EVT have excluded patients with BP above 185/110 mmHg (as such patients were potential candidates for rt-PA), though the conclusions from these studies are limited [33, 34, 43–46].

It is justified in patients after rt-PA administration eligible for thrombectomy to maintain BP below 180/105 mmHg to mitigate the risk of haemorrhage. In patients eligible to endovascular treatment only, the current guidelines suggest that maintaining BP \leq 185/110 mmHg before the procedure is “reasonable” [15]. Nevertheless, the benefits of BP lowering in the pre-reperfusion time are uncertain and are not supported by the literature [32, 47]. In another study, BP reduction before recanalisation was associated with larger infarct volumes and worse functional outcomes at discharge and at 90 days [48]. The MR CLEAN post-hoc study showed that a decrease in MAP during the intervention under general anaesthesia (GA) compared to baseline BP was associated with a worse outcome. On the other hand, analysis of the SIESTA trial has shown that there is no association between BP parameters (SBP, diastolic blood pressure (DBP), MAP) from baseline to the different phases of intervention (i.e. preintervention, prerecanalisation, postrecanalisation and postintervention) and NIHSS score at 24 h after thrombectomy [47]. Nor was there any association between BP drops and 3-month mRS outcome.

Secondary analysis of data from the GOLIATH trial, in which patients were randomised to undergo endovascular therapy with GA or conscious sedation (CS), examined the relationship between variables related to blood pressure and adverse neurological outcome [49]. There were no statistically

significant associations between BP-related variables and adverse neurological outcomes. In both the GOLIATH and SIESTA trials, strict BP thresholds were applied: SBP \geq 140 mmHg and MAP \geq 70 mmHg according to the recommendations from the Society for Neuroscience in Anaesthesiology and Critical Care [50] and the study by Whalin et al. [51], who reported poor outcomes below this threshold. Such predefined treatment targets of SBP and MAP may explain the neutral results in GOLIATH and SIESTA. In contrast, patients included in the MR CLEAN study [32] were presented with median admission BP of 140 mmHg, meaning that 50% of included patients had admission BP levels lower than the minimum level recommended by the Society of Neuroscience in Anaesthesiology and Critical Care [50].

The significance of the type of anaesthesia during EVT has also been a matter of debate. Although retrospective studies have reported worse outcomes with GA and it being associated with hypotension and unstable haemodynamics [51, 52], analysis of three recent randomised trials [47, 49, 53] all investigating peri-interventional management in patients divided into groups of GA and CS, has reported no difference in the primary outcome parameters (90 days 0–2 mRS and NIHSS at 24 h) between groups. The currently ongoing MASTERSTROKE study, assessing two hemodynamic targets during EVT from the beginning of anaesthesia to the moment of recanalisation, might provide an interesting perspective. The pilot trial showed no differences in early neurological improvement,

all-cause mortality at 90 days, intraoperative complications or intracerebral haemorrhage rates between patients in two BP target groups (130–150 mmHg and 160–180 mmHg) [54].

The subsequent aspect of BP management during EVT is the post-reperfusion time. Studies show that BP drops spontaneously shortly after successive reperfusion therapy and BP decline is not associated with a worse outcome, whereas in non-recanalised patients, BP drops to the same levels but after a longer time [55, 56].

The guidelines recommend maintaining BP after EVT below the level of 180/105 mmHg. However the expert opinion in EVT is to lower BP to 140/90 mmHg in patients with successful reperfusion, aiming to prevent cerebral haemorrhage and reperfusion injury as it was conducted in the DAWN trial [57]. Recent studies seem unanimous in concluding that higher BP values 24 hours after thrombectomy are associated with worse functional outcomes (Tab. 1) [37, 38, 58–60]. However, an association between BP parameters and haemorrhagic complications is less evident [37, 60]. In the groups of patients with successive reperfusion, achieving BP < 160/90 mmHg during the first 24 h post-EVT was independently associated with a lower likelihood of 3-month mortality compared to the group with higher maximum BP values [37]. In successfully recanalised patients, haemorrhagic complications were observed at lower mean values of maximum SBP [38]. In theory, permissive hypertension may benefit patients with non-recanalised LVO by maintaining cerebral perfusion pressure through the

Table 1. Observational studies examining impact of blood pressure during first 24 hours after mechanical thrombectomy in acute ischaemic stroke

Study	Patients and study therapeutic targets	BP parameter	Main findings
Goyal et al. [37]	All: n = 217; TICI \geq 2b: n = 145	SBP, DBP mean	10 mmHg increment in max SBP associated with lower likelihood of functional independence (OR = 0.7, CI 0.56–0.87, p = 0.001) and higher odds of mortality (OR = 1.49, CI 1.18–1.88, p = 0.001) Achieving BP < 160/90 mmHg in patients with TICI \geq 2b is associated with lower mortality (p = 0.01, OR = 0.08) No difference in max SBP in patients with or without sICH in whole cohort or in group with TICI \geq 2b
Mistry et al. [38]	All: n = 228; TICI \geq 2b: n = 156	SBP, DBP, MAP max, min, mean	Max SBP correlated with worse 90-day outcome (OR = 1.02, CI 1.01–1.03, p = 0.004) and haemorrhagic complications (OR = 1.02, CI 1.01–1.04, p = 0.002) In patients with TICI \geq 2b, max SBP correlated with worse mRs (OR = 1.02, CI 1.00–1.03, p = 0.01) and severity of haemorrhagic complications (OR = 1.02, CI 1.00–1.03, p = 0.05) Correlation between haemorrhagic complications and max SBP (OR = 1.05, CI 1.01–1.1, p = 0.01) and max MAP (OR = 1.06, CI 1.01–1.11, p = 0.02) in patients with TICI < 2b
Cernik et al. [60]	All: n = 690; TICI \geq 2b: n = 551	SBP, DBP max, mean	Patients with mRs 0–2 had a lower median of SBP (p < 0.0001) and a median of max SBP (p < 0.0001) compared to those with mRs 3–6 Similar results were found in group with TICI \geq 2b (p < 0.0001) No significant difference in SBP levels between those with good and poor outcome in patients with TICI < 2b No difference in rate of sICH between patients with median SBP < 140 and \geq 140 mmHg
Goyal et al. [61]	TICI < 2b: n = 88	SBP, DBP max, min	Max SBP (OR = 0.55, CI 0.39–0.79, p = 0.001) and min SBP (OR = 1.64, CI 1.04–2.6, p = 0.033) were associated with odds of functional independence (mRs 0–2) Min SBP (OR = 0.65, CI 0.47–0.9, p = 0.009) and max DBP (OR = 1.61, CI 1.1–2.36, p = 0.014) were associated with mortality No difference between max SBP and DBP and occurrence of sICH

DBP — diastolic blood pressure; MAP — mean arterial pressure; mRs — modified Rankin scale; SBP — systolic blood pressure; sICH — symptomatic intracerebral haemorrhage; TICI — thrombolysis in cerebral infarction scale

Table 2. Observational studies examining impact of blood pressure variability after mechanical thrombectomy in acute ischaemic stroke

Study	N	BP parameters	Results	
			Primary outcome	sICH
Mistry et al. [72]	443	SBP, DBP SD, CV, ARV, SV, rSD	All BPV indices were significantly higher in patients with poor outcome or death Highest tertile of SBP variability predicted poor outcome (OR 1.8–3.5, all $p < 0.05$) BPV was lowest in patients who did not receive any intravenous medications ($p < 0.001$)	No association between BPV and sICH
Bennett et al. [73]	182	SBP, DBP, MAP SD, CV, SV	SBP indices at 0–24, 0–48 and 0–72 h were associated with a 1-point increase in follow up mRS (OR 2.3–4.38, $p < 0.002$) Systolic SV was best predictor of a 1-point increase in mRS (OR 2.63–3.23, all $p < 0.007$) No consistent association between DBP or MAP and outcome was observed	No association between BPV and sICH

ARV — average real variability; BPV — blood pressure variability; CV — coefficient of variation; DBP — diastolic blood pressure; MAP — mean arterial pressure; mRS — modified Rankin Scale; rSD — residual standard deviation; SBP — systolic blood pressure; SD — standard deviation; sICH — symptomatic intracerebral haemorrhage; SV — successive variation

collaterals. However, this notion is contradicted by studies that have shown an association between high SBP and DBP and an increased likelihood of 3-month mortality and poor outcome [60, 61]. The study authors concluded that future larger studies should examine the potentially beneficial effect of permissive hypertension following EVT in subgroups of patients with sufficient collaterals status and high ASPECTS scores.

Blood pressure variability

The importance of blood pressure variability (BPV) in ischaemic stroke patients has been a matter of debate for the last 20 years. This can be defined as beat-to-beat variability, 24-hours variability, day-to-day variability, or over the longer term — visit-to-visit variability.

Studies show that higher BPV is associated with worse long-term outcomes and mortality after acute stroke [56, 62, 63]. The study by Minhas et al. [64] enrolling over 8,000 ischaemic stroke patients indicated that coefficient of variation (CV) SBP over 24 hours after acute onset had a significant linear association with unfavourable shift in 90 days mRS. By contrast, results regarding short-term outcomes or recurrent stroke are conflicting [65, 66]. However, there is no consensus regarding the most reliable haemodynamic parameter (SBP, DBP, MAP or pulse pressure (PP)) and the variability index or as to the exact thresholds which exceeding might result in an unfavourable outcome [67, 68].

A meta-analysis of the long-term prognostic significance of BPV was attempted by Appiah et al., but unfortunately the methodological heterogeneity of the assayed studies and their incomplete reporting made this impossible [68]. Nonetheless, in the studies considered, the most frequently used BPV parameters were CV, successive variation (SV), standard deviation (SD), and the difference maximum-minimum. The main haemodynamic parameters measured were SBP and MAP. The relevance of PP fluctuations in AIS has been underexplored. Sparse studies show that PP variability, more than SBP variability, is associated with worse outcome after

stroke [66, 69]. PP as a pulsatile component of BP and a presumed marker of stiffness may better describe haemodynamic changeability [70].

The association between BPV and outcome has been better reported in studies enrolling patients after reperfusion [62, 63, 71–73] or BP-lowering therapies [63]. In patients after IVT, BP changes were independently associated not only with outcome, but also with sICH and death [62, 71]. Some studies have demonstrated that the impact of BPV on outcome varied depending on the recanalisation status, with a significant association observed only in the non-recanalised group [56, 74]. Similar results have been achieved in groups of patients after EVT, although an association between BPV and sICH is lacking (Tab. 2) [72, 73]. A decline in blood pressure before recanalisation has been associated with larger volumes and worse functional outcomes for patients affected by an LVO stroke [48]. Apart from recanalisation status, it seems that the collateral circulation might be of importance concerning BPV and outcome. In Chang's study, most BPV parameters remained significant in predicting early deterioration and poor 3-month outcomes in patients with poor collateral circulation [75], whereas no significant association was found between BPV parameters and clinical outcomes in patients with good collateral circulation. Interestingly, in the same study, most BPV parameters were significantly higher in patients with internal carotid artery (ICA) occlusion than in those with MCA occlusion. The explanation may be decreased baroreceptor reflex in patients with ICA occlusion that causes sympathetic overactivity inducing high BPV.

Future directions

There is scarce evidence about managing BP in AIS, and this provides researchers with extensive opportunities for further studies. We recommend considering the following aspects in future trials:

1. BP management in peri-reperfusion time

- The significance of baseline BP in EVT and pre-reperfusion permissive hypertension is uncertain, and requires further research.
 - There is a substantial need for RCTs of optimal BP management in peri-procedural time of endovascular treatment. In studies concerning intra-procedural BP management, pre- and post-reperfusion time intervals should be differentiated and considered separately.
 - Analysis should distinguish between patients with different recanalisation statuses, since each group may have disparate BP requirements.
2. Neurovascular monitoring/imaging
 - Imaging techniques, e.g. TCD, may be of some value in precise BP control according to blood flow parameters, but further research is necessary.
 - The importance of compliance with collaterals and BP management is not yet determined, and should be further studied.
 3. Euvolemia as a therapeutic target
 - The role of rehydration of dehydrated acute stroke patients in improving clinical outcomes needs further trials.
 4. Blood pressure variability
 - Future RCTs investigating BPV reduction after reperfusion therapies are needed to assess their utility as a novel therapeutic target after stroke.
 - BPV should be measured in the short term (minutes and hours) and in the longer term (day-by-day and visit-to-visit) and include different BPV parameters.
 - Authors should provide detailed information about their study populations and the employed BP regulation during the observation time, including the class of medications used, so as to enable future meta-analysis.

Conclusions

BP management is an important and challenging aspect of care in acute stroke patients. Although the U-shaped association between BP values during the acute period and functional outcome has been verified, no benefits have been found of active BP correction. The current guidelines differentiate BP targets on the basis of employed reperfusion treatment, and allow BP reduction in only a few clinical situations.

However, topical literature shows that personalised, autoregulation-based BP targets, compared to static systolic BP thresholds, might be of greater value in order to achieve the best functional outcome and avoid detrimental events. The optimal BP goal may exist, but it is questionable whether a one-size-fits-all approach is reasonable. Future trials considering patient-specific factors with the use of continuous BP and neurovascular monitoring may provide some answers.

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