

## Current and Emerging Concept

# Management of Hypertension in the Setting of Acute Stroke: A Literature Review

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### Abstract

Stroke is still a highly prevalent complication of hypertension and cause of death in the Philippines and in the rest of Southeast Asia. Management of acute elevation of the blood pressure (BP) can be a challenge which can impact both short- and long-term outcomes. The dilemma of allowing or not some degree of “permissive hypertension” in an acute stroke is a question every clinician is confronted with. This paper aims to summarize the recent guidelines on BP management in the setting of acute stroke based on the recommendations of three international guidelines, namely the American College of Cardiology/American Heart Association (ACC/AHA), European Society of Cardiology/European Society of Hypertension (ESC/ESH), and the Canadian Stroke Best Practices. It also reviews the major randomized controlled trials and other publications evaluating the management of BP elevation in an acute stroke setting. The updated guidelines in the ACC/AHA, ESC/ESH, and Canadian best practice have no significant difference in their recommended BP threshold for intervention. In general, BP lowering is not recommended unless BP is  $\geq 220/110$  mmHg. However, in patients who are eligible for intravenous (IV) thrombolysis and have very high systolic BP (SBP)  $\geq 185$  mmHg or diastolic BP  $\geq 110$  mmHg, cautious BP lowering should be done before IV thrombolysis and should be maintained during the treatment duration. In the acute BP management of intracerebral hemorrhage (ICH) earlier guidelines favored lowering of BP to  $<140$  mmHg, SBP based on a large randomized controlled trial – the Intensive BP reduction in acute cerebral hemorrhage (INTERACT) trial 2. On the other hand, outcomes of the antihypertensive treatment in ATACH-2 trial showed a significantly higher rates of neurological deterioration within 24 h in those with reduced and renal events and pneumonia was higher in the group where intensive BP management was instituted. In general, clinical practice guidelines advocate that in those with acute ICH and SBP between 150 and 220 mmHg, reducing SBP to  $<140$  mmHg within 6 h is not beneficial in terms of death and functional outcome and can be potentially harmful. In acute ICH and SBP  $>220$  mmHg, it is reasonable to lower BP with IV therapy to around 180 mmHg.

**Key words:** Hypertension management in acute stroke, permissive hypertension, spontaneous intracerebral hemorrhage

### Introduction

The burden of stroke has not been mitigated over the past 2–4 decades. In terms of the proportions of disability and mortality as a result of stroke, the less developed regions of the world surpass most developed nations.<sup>[1]</sup> The primary causes of the increased global burden of stroke are related to the increase in stroke risk factors, particularly hypertension. Part of the reason for the higher disability and mortality rates is probably in the lack of

understanding on how best to manage the blood pressure (BP) in different stroke settings.<sup>[2,3]</sup>

In general, acute ischemic strokes (AISs) account for 80% of the stroke cases while hemorrhagic strokes account about 20% depending on the specific population. Recent data from the Risk Factors for Ischemic and Intracerebral Stroke in 22 Countries (INTERSTROKE) study, which included the Philippines, China, Malaysia and Sudan showed that the proportions of ischemic and

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hemorrhagic stroke in Southeast Asia were about 78% and 22%, respectively, compared to about 91% of ischemic stroke and 9% of hemorrhagic stroke in high-income countries.<sup>[4,5]</sup>

How to manage the elevated BP in these two conditions in the acute setting is challenging in clinical practice, and this has been tackled by various guidelines over the last several years.<sup>[6]</sup> Understanding the principles of BP management in acute stroke according to the best evidence based on the latest and better-designed research outcome results are important. However, in certain circumstances, an individualized approach to the BP management on a specific stroke patient may be necessary.

While the guidelines on BP management in AIS are fairly uniform in most guidelines, this has been challenging in hemorrhagic strokes. Spontaneous, non-traumatic intracerebral hemorrhage (ICH) still is a major reason of morbidity and mortality across all countries. Even though ICH has been behind in terms of clinical trials that will help in the management as compared to other types of strokes (ischemic and subarachnoid hemorrhage), there was a significant increase of researches regarding ICH in the past decades.

The recent guidelines in BP management of acute stroke in the acute setting are reviewed here. Review of some recent clinical trials, not included or reviewed in the current guidelines were also analyzed.<sup>[7-11]</sup>

## BP Management in AIS

Acute hypertension management in the setting of an AIS is as important as giving intravenous (IV) thrombolysis or initiating antithrombotic agents. There are several studies and guidelines that discuss management of elevated BP in AIS. Recommendations depend on the following: Whether or not patients are eligible for thrombolysis or not, presence of comorbid conditions, and presence of hypotension.

In the 2018 American Heart Association (AHA)/ASA Guidelines for the Early Management of Patients with AIS,<sup>[12]</sup> for patients not eligible for IV thrombolysis, acute BP lowering is not recommended unless the BP is  $\geq 220/110$  mmHg. Exceptions are patients who have comorbid conditions that require lowering of BP. Starting or restarting management of hypertension for the first 48–72 h post-ictus is not successful to avoid death or dependency. For those who are eligible for IV thrombolysis and who have very high BP ( $>185$  mmHg systolic blood pressure [SBP] or  $>110$  mmHg diastolic blood pressure [DBP]), BP should be cautiously reduced to an SBP of  $<185$  mmHg and DBP to  $<110$  mmHg before initiating IV fibrinolytic therapy. For those patients, that is, for possible intra-arterial therapy and for those who were not given IV thrombolytic therapy, it is acceptable to sustain BP  $\leq 185/110$  mmHg before the procedure.<sup>[12]</sup>

During the first 24 h post-ictus, it is acceptable to decrease BP by 15%. However, there are no concrete evidence existing in terms of medication selections for BP lowering. Initiating or reinitiating BP lowering agents during admission in patients with BP  $>140/90$  mmHg who are neurologically stable are

harmless and are acceptable to achieve better long-standing BP control not unless contraindicated. It is also necessary to avoid and correct hypotension and hypovolemia to ensure adequate systemic circulation essential for maintenance organ function.<sup>[12]</sup>

In the 2018 Canadian Recommendations for Acute Stroke Management, similar BP recommendations are given to ischemic stroke patients eligible for thrombolytic therapy.<sup>[13]</sup> Markedly elevated BP  $>185/110$  mmHg should be managed before IV thrombolysis to lower the possibility of hemorrhagic conversion. BP should be lowered and sustained  $<185/110$  mmHg before alteplase therapy and  $<180/105$  mmHg within the next 24 h after giving alteplase. In patients with ischemic stroke not qualified for thrombolysis, acute BP lowering is not recommended. Extreme BP elevation (e.g., SBP  $>220$  mmHg or DBP  $>120$  mmHg) must be managed accordingly to lower down the BP by around 15%, and not  $>25\%$ , within the first 24 h with additional steady lowering afterward to desired level for continuing secondary stroke prevention, although the ideal BP level to reach and maintain in the hyperacute phase is unknown at this time. It is a good practice to avoid rapid or excessive lowering of BP because this may aggravate present cerebral ischemia specifically in patients with intracranial or extracranial arterial obstruction.<sup>[13]</sup>

In the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guidelines for the treatment of hypertension in AIS, regular BP lowering is not advocated with the following exceptions: (a) Patients with AIS who are candidates for IV thrombolysis, BP must be judiciously reduced and sustained at  $<180/105$  mmHg within the first 24 h after IV rTPA and (b) patients with significantly elevated BP who were not given IV rTPA, BP lowering agent may be contemplated, based on clinical judgment, to lower down BP by 15% within the first 24 h post-ictus.<sup>[14]</sup> A comparative summary of the hypertension management in the acute setting recommendations from three different guidelines is shown in Table 1.

In the 6<sup>th</sup> edition of the Stroke Society of the Philippines (SSP) Handbook for Stroke Prevention, Treatment, and Rehabilitation in 2014, it is recommended treating with an antihypertensive agent if mean arterial pressures (MAPs) are  $>130$  mmHg, avoiding a precipitous drop in BP (not  $>15\%$  of baseline MAP) within 24 h. Moreover, if drug treatment is needed, IV antihypertensive agents (which include nicardipine, hydralazine, labetalol, or esmolol) or short-acting ones are preferred.<sup>[15]</sup>

In the Enhanced Control of Hypertension and Thrombolysis Stroke Study,<sup>[16]</sup> intensive BP lowering ( $<140/90$  mmHg) was significantly less likely to suffer intracranial hemorrhages. It also showed that mRS score distribution within 90 days was not different across clusters. There were lesser patients in the intensive cluster as compared to the guideline cluster who had intracranial hemorrhage. The proportion of patients with any severe unfavorable incident was not significantly different among the intensive cluster and the guideline cluster. There was no indication of a relationship between intensive BP lowering and the dose (low vs. standard) with alteplase in terms with primary outcome.<sup>[16,17]</sup>

**Table 1:** Summary of the different guidelines in the hypertension management in acute ischemic stroke

Guidelines	Eligible for thrombolysis	Not eligible for thrombolysis	Other compelling indication
2018 Guidelines for the early management of patients with acute ischemic stroke (ACC/AHA)	BP must be carefully decreased to SBP of <185 mmHg and DBP of <110 mmHg before giving IV fibrinolysis Until new data will be at hand, in patients eligible for intra-arterial therapy is planned without IV thrombolysis, it is acceptable to maintain BP ≤185/110 mmHg before the procedure	Patients with BP <220/120 mmHg who was not given IV alteplase or EVT without any disease needing acute BP lowering medications, starting or restarting medication within the first 48–72 h post-ictus is not successful to prevent death or dependency Patients with BP ≥220/120 mmHg who was not given IV alteplase or EVT, without disease needing acute BP lowering treatment, the advantage of starting or restarting medications for hypertension within the first 48–72 h is unknown. However, it might be acceptable to decrease BP by 15% within the first 24 h post-ictus	
2018 Canadian stroke best practice recommendations for acute stroke management	The blood pressure needed to attain and maintain in the hyperacute phase is uncertain as of the moment Patients who are for thrombolysis: BP >185/110 mmHg must be managed together with thrombolysis to decrease the possibility of hemorrhagic conversion. Blood pressure must be decreased and maintained <185/110 before giving alteplase and to <180/105 mmHg for the next 24 h post-thrombolysis.	Management of hypertension in patients with acute ischemic stroke or TIA should not be routinely managed	SBP >220 mmHg or DBP >120 mmHg must be managed to lower down the blood pressure around 15%, but not >25%, within the first 24 h. After which, further slow reduction to targets for long-term secondary stroke prevention
2018 ESC/ESH Guidelines for the management of arterial hypertension	BP must be cautiously decreased and sustained at <180/105 mmHg for at least 24 h post-thrombolysis	BP can be reduced by 15% based on clinical judgment within the first 24 h post-ictus	

TIA: Transient ischemic attack, ACC: American College of Cardiology, AHA: American Heart Association, ESC: European Society of Cardiology, ESH: European Society of Hypertension, BP: Blood pressure, DBP: Diastolic blood pressure, IV: Intravenous, SBP: Systolic blood pressure

## BP Management in Acute Hypertensive ICH

In patients with spontaneous ICH, elevated BP is common in the acute setting due to several factors which include the following: Stress, pain, elevated intracranial pressure, and history of an acute or continuous increase in BP. It is related with bigger hematoma enlargement, neurological worsening, and death and dependency after ICH.<sup>[14]</sup> In contrast with AIS, in which consistent U- or J-shaped associations between SBP nadir of 140 and 150 mm Hg and poor outcome have been shown, only 1 study of ICH has shown a poor outcome at low SBP levels (<140 mm Hg).<sup>[18]</sup> Both the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH1) trial<sup>[19]</sup> and the pilot phase Intensive BP Reduction in Acute cerebral hemorrhage trial (INTERACT1)<sup>[20]</sup> showed lowering of SBP to <140 mmHg to be safe. The INTERACT2 trial did not demonstrate a rise in death or severe adverse outcomes in early aggressive BP lowering.<sup>[21]</sup>

The INTERACT2 is one of the biggest randomized clinical trials in the ability of intensive BP reduction, in which ICH patients (6 h post-ictus) with SBP between 150 and 220 mmHg (52.0% intensive treatment group with SBP target of <140 mmHg and 55.6% in the standard treatment group SBP <180 mmHg) with principal result of death or major disability. For the secondary end points, it revealed that there is significantly improved

functional recovery based on the mRS and superior physical as well as mental health-related quality of life based on the EQ-5D scale in the intensive group. While this study showed promising treatment effect, there was no strong association between outcome and ICH ictus onset to starting treatment. There was also no substantial influence of intensive BP reduction on hematoma expansion. Furthermore, it was found out that one-third of patients who attained the intended SBP level in 1 h and the other half attained the goal at the 6<sup>th</sup> h, and majority (75%) only have mild-to-moderate volume (<20 mL) of hematomas.<sup>[21]</sup>

In the 2017 American College of Cardiology (ACC)/AHA/Guidelines, those with SBP >220 mmHg, it is reasonable to start continuous IV medication infusion with judicious BP monitoring. However, immediate lowering SBP to <140 mmHg in those patients 6 h post-ictus with SBP ranging from 150 to 200 mmHg, it was found out that there is no benefit in terms of reduction of mortality or severe incapacitation and may even be evenly potentially harmful.<sup>[22]</sup>

In the 2018 ESC/ESH Guidelines for the treatment of hypertension in patients with spontaneous ICH, results from a randomized control trial suggested that immediate lowering of blood pressure (within 6h) to <140/90 mmHg did not show benefit on the primary outcome of disability or death at

3 months, but might decrease hematoma expansion, improve functional outcome, and was generally safe.<sup>[14]</sup> Another RCT, wherein SBP was immediately decreased (<4.5 h) from an average of 200 mmHg to two different goals (140–170 vs. 110–139 mmHg), revealed that aggressive BP lowering still shows no added advantage on the same primary effect and with additional renal adverse consequences. Therefore, immediately decreasing the BP in ICH is not recommended but with some exception: Acute ICH with SBP  $\geq$ 220 mmHg, although there is still a paucity of data in this type of patients. Consequently, cautiously decreasing the BP through IV infusion may be started.<sup>[14]</sup>

In the 6<sup>th</sup> edition of the SSP Handbook for Stroke Prevention, Treatment, and Rehabilitation in 2014, it is recommended that treating hypertension if SBP >180 mmHg and lowering it to 140 mmHg within 7 days is safe and improves outcome in patients with small to moderate-sized ICH not requiring surgical intervention.<sup>[15]</sup>

In the recent BP-attained analysis of ATACH 2 trial, the proportions of deterioration within 24 h were considerably greater in patient with reduced and sustained SBP of <140 as well as in reduced SBP (within 2 h) but not maintained group in comparison with the reference. In comparison for those patient without control of BP, there are higher proportions of cardiac-related complications within 7 days among patient with reduction and maintenance of SBP <140.<sup>[23]</sup>

## Discussion

The optimal level of BP that should be maintained in patients with AIS is still not well established.<sup>[12]</sup> Moreover, no RCTs have focused on the management of low BP in stroke. In a systematic analysis (12 studies), it showed that the chances of death or dependence were the same when using either colloids or crystalloids.<sup>[12]</sup>

BP management depends on whether a patient is eligible or not for IV thrombolysis as well as the presence of any compelling indication to lower down BP early in the acute setting of stroke. For most cases who are not eligible for IV thrombolysis, there is no hurry to bring down the BP in the first few hours after the ictus.

Accordingly, the ACC/AHA, ESC/ESH, and Canadian guidelines agreed to lower BP to <185/105–110 mmHg if a patient is a candidate for IV thrombolysis. In patients with  $\geq$ 220/110 mmHg who are not eligible for IV thrombolysis, lowering of BP should be kept to 15–25% reduction during the first 24 h of stroke.

Although the choice of antihypertensive agents used during the acute phase of ischemic stroke is still uncertain, IV antihypertensive agents seem reasonable due to their fast onset of action and can be easily titrated to achieve the goal BP level. These agents include nicardipine, labetalol, and urapidil. After the acute period of ischemic stroke, an oral antihypertensive should be started as a secondary prevention of not only ischemic stroke but also ICH as well. However, the

choice of the long-acting oral antihypertensive agents will still depend on several factors such as comorbidities and age. In the ESC/ESH guidelines, a single-pill combination of a renin-angiotensin system blocker plus a calcium channel blocker or thiazide or thiazide-like diuretic is recommended as initial management for the majority of hypertensive patients. In the Canadian hypertension guidelines, for patients with diabetes with cardiovascular disease risk or chronic kidney disease, an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) is considered to be the preferred first-line agents. For patient with coronary artery disease, ACEi or ARB and beta-blockers are recommended as good choices. For patients with past stroke or transient ischemic attack, ACEi and/or thiazide diuretic are recommended.

In patients with ICH, the current evidence is less clear whether early intensive BP lowering is really safe. The more recent analysis of ATACH 2 trial is not congruent with the findings seen in INTERACT2 trial. While there is no decline in death or disability, there are signals of harm as shown by higher rates of neurological deterioration and cardiac-related adverse effects in patients with ICH receiving early intensive BP-lowering treatment.<sup>[23]</sup>

## Conclusion

BP management in the setting of AIS and spontaneous ICH is different from the treatment of other hypertensive situations such as hypertensive urgencies and emergencies as well as in the secondary prevention of stroke. Treatment depends on several factors such as timing, comorbidities, and eligibility for thrombolysis. This review of selected research articles and current guidelines on the management of hypertension in acute stroke setting hopes to improve one's understanding of the uniqueness of BP management of the acute phase compared with the non-acute phase both in ischemic and hemorrhagic strokes.

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