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The 2020 Taiwan Stroke Society guidelines for blood pressure control at the acute stage of ischemic stroke

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The 2020 Taiwan Stroke Society (TSS) guidelines for blood pressure (BP) control related to ischemic stroke update the 2015 TSS BP guidelines. The early management of acute ischemic stroke has evolved rapidly in the previous two decades. Since the publication of the previous version of the TSS BP guidelines, many studies have addressed BP management in ischemic stroke. Particularly, several successful endovascular thrombectomy (EVT) trials published in 2015 led to a new era of acute treatment for ischemic stroke. With the ever-increasing use of EVT, evidence-based guidelines for ideal BP management during and after EVT are urgently needed. Consequently, the 2020 guidelines are updating and providing recommendations on BP control for the treatment and prevention of ischemic stroke based on new evidence. The present study encompasses the most important chapter of the 2020 Taiwan BP guidelines: BP control at the acute stage of ischemic stroke. We incorporated the most updated evidence

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regarding BP control at the acute stage of ischemic stroke in patients receiving or not receiving acute reperfusion therapy and provided specific recommendations for different treatment subgroups accordingly.

Contents

Introduction

The application of acute reperfusion therapy, including intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT), has significantly changed the early management of acute ischemic stroke in the recent two decades. Therefore, blood pressure (BP) control in the acute stage of ischemic stroke nowaday becomes more complicated than solely permissive hypertension, which was usually adopted previously. The major purpose of this guideline is to provide recommendations to healthcare professionals dealing with acute ischemic stroke in Taiwan based on the most updated scientific evidence.

According to the American Heart Association and American Stroke Association (AHA/ASA), each recommendation was designated with a Class of Recommendation (COR) and a Level of Evidence (LOE). The COR indicates the strength of the recommendation based on the estimated magnitude and certainty of benefits versus risks. The LOE indicates the quality of scientific evidence supporting the management based on the type, quantity, and consistency of the data from the identified studies. The COR and LOE interpretations are shown in Tables 1 and 2 respectively.

All recommendations in this guideline provide the common principles for BP control at the acute stage of ischemic stroke. Due to the highly variable clinical conditions in this acutely ill population, the BP management in each patient should be considered individually, based on their physicians' clinical decisions.

General concepts

Elevated BP is common in the acute phase of ischemic stroke. Previous observational studies have indicated that 77% of patients with ischemic stroke have a systolic BP $>$ 139 mmHg and 15% have a systolic BP of over 185 mmHg.[1] However, there is no consensus regarding BP control policies during the acute phase. Although some studies have pointed out that higher BP is associated with poor prognosis,[2,3] stroke experts still doubt whether lowering BP after ischemic stroke would lead to insufficient cerebral perfusion and worsening of cerebral infarction; therefore, there is no consistent opinion on the goal of antihypertensive treatment for this stage.[4]

A European randomized controlled trial (Intravenous Nimodipine West Europe Stroke Trial, INWEST) compared the use of intravenous nimodipine to lower BP within 24 h of ischemic stroke with standard treatment and found that the 21-day functional prognosis (Barthel scale) of the treatment group was significantly worse than that of the control group ($p = 0.003$).[5] Another Scandinavian randomized controlled trial (The Angiotensin-receptor Blocker Candesartan for Treatment of Acute Stroke) pointed out that using candesartan to lower BP within seven days of disease onset did not significantly reduce the six-month vascular event rate in patients with ischemic stroke (HR, 1.09; 95% CI, 0.84–1.41).[6] A Chinese randomized controlled trial (China Antihypertensive Trial in Acute Ischemic Stroke,

Table 1 Class of recommendation.

Class of Recommendation	Interpretation	Phrases used in recommendation
Class I	Benefit >>> Risk	Is recommended/ suggested/indicated
Class IIa	Benefit >> Risk	Is reasonable; can be beneficial/ effective
Class IIb	Benefit ≥ Risk	May/Might be reasonable/ considered
Class III	Benefit < Risk	Is not recommended/ suggested/ indicated; May be harmful

Table 2 Level of evidence.

Level of Evidence	Interpretation
Level A	1. High-quality evidence from more than 1 RCT 2. Meta-analyses of high-quality RCTs
Level B − R	1. Moderate-quality evidence from 1 or more RCTs 2. Meta-analyses of moderate-quality RCT
Level B − NR	1.Moderate-quality evidence from 1 or more well-designed non-randomized studies, observational studies or registries 2. Meta-analyses of such studies
Level C − LD	1. Evidence from studies with limitation of design or execution 2. Meta-analyses of such studies
Level C − EO	Consensus of experts

EO, expert opinion; LD, limited data; NR, non-randomized; R, randomized; RCT, randomized controlled trial.

CATIS) found that, compared with withholding all BP medications after the onset, using BP medication within seven days of acute ischemic stroke to maintain a BP below 140/90 mmHg did not reduce the risk of death and significant disability within 14 days (odds ratio [OR], 1.00; 95% CI, 0.88−1.14).[7] Therefore, there are no general guidelines for BP control during the acute phase of ischemic stroke. However, with the development of treatment methods for the acute phase of ischemic stroke, many new studies have focused on BP control in specific groups receiving different treatments. These findings will challenge the generous BP control goals in the acute phase of ischemic stroke used in the past. The following is a discussion of the populations in different situations.

BP control in patients not receiving reperfusion therapy

For patients who have not received reperfusion therapy, no reliable evidence currently supports precise BP control. According to the acute stroke treatment guidelines published by the European Stroke Society in 2008 and updated by the AHA/ASA in 2018, the general consensus remains that aggressive BP lowering is not required in the acute phase if BP does not exceed 220/120 mmHg, unless there are comorbidities requiring urgent treatment.[8,9] If the BP is greater than 220/120 mmHg and antihypertensive therapy is required, it is recommended to decrease the initial systolic BP to within 15% and closely monitor the neurological deficits.

BP control in patients receiving IVT

BP control before IVT

The current goal of BP control before IVT was derived from the original National Institute of Neurological Disorders and Stroke rt-PA Stroke Study, in which the research team referred to the past experience of thrombolytic therapy for myocardial infarction and set a BP greater than 185/110 mmHg as an exclusion condition.[10,11] According to the guidelines of the AHA/ASA published in 2018, patients who are expected to receive IVT should control their BP to below 185/110 mmHg before treatment.[8]

BP control after IVT

According to the guidelines of the AHA/ASA published in 2018, BP within 24 h after IVT should be controlled to below 180/105 mmHg.[8] A large-scale stroke registration trial (Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry, SITS-ISTR) found that patients with systolic BP greater than 170 mmHg were four times more likely to have symptomatic intracranial hemorrhage, while the chance of having functional autonomy after treatment was reduced by half[12] compared to that of patients with systolic BP of 141−150 mmHg. Moreover, previous observational studies have pointed out that violating the BP targets recommended by the guidelines increases the risk of symptomatic intracranial hemorrhage.[13,14] In 2019, a large-scale meta-analysis of 26 studies on BP control and prognosis after IVT was conducted for ischemic stroke. A total of 56,513 patients were included in the analysis. The results showed that higher systolic BP after treatment was associated with symptomatic intracranial hemorrhage (OR, 1.13; 95% CI, 1.01−1.25), and there was a lower probability of functional independence (modified Rankin scale [mRS] 0−2) for three months (OR, 0.70; 95% CI, 0.57−0.87).[15] However, although this study showed the benefit of controlling BP at a lower level after IVT, it failed to provide a target value for BP control in clinical practice.

The Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) is a large multinational randomized clinical trial with a dual-arm design that investigates the dose of intravenous thrombolytic agents and BP control after treatment. The second arm, which explored BP control, was published in 2019. The study divided 2196 patients receiving IVT 1:1 into the active BP group (systolic BP, 130−140 mmHg) and standard BP control group (systolic BP < 180 mmHg) recommended by the

guidelines and monitored for 72 h. The final average systolic BP of the two groups was 144.3 and 149.8 mmHg, respectively. The results showed that the 3-month functional prognosis (mRS distribution) between the two groups was not significantly different (OR, 1.01; 95% CI, 0.87—1.17). Conversely, the active control group had a significantly lower risk of intracranial hemorrhage than the standard control group (OR, 0.75; 95% CI, 0.60—0.94), but there was no significant difference in terms of symptomatic intracranial hemorrhage (OR, 0.65; 95% CI, 0.33—1.28).[16] This study showed that it is safe to control BP lower than that recommended by the guidelines after IVT, but it does not significantly improve the functional prognosis. It is worth mentioning that the actual difference in systolic BP between the two groups in this study (144 vs. 150 mmHg) was not as good as that in the original design (130—140 vs. <180 mmHg), which may be one of the reasons for the insignificant difference in prognosis.

Table 3 listed the proposed BP targets for different stages of IVT.

In addition to the absolute BP, fluctuations in BP have also been found to be related to the prognosis after IVT. A cohort study on 427 patients with ischemic stroke undergoing IVT analyzed the parameters (successive variation [SV]) of BP fluctuations within 20—36 h after treatment and found that higher BP fluctuations predicted poor 3-month mean mRS scores (OR, 1.68; 95% CI, 1.05—2.69), but were not significantly related to symptomatic intracranial hemorrhage.[17] Another cohort study of 461 patients with ischemic stroke undergoing IVT analyzed the standard deviation of systolic BP and SV within 24 h. The standard deviation of systolic BP and systolic BP SV was significantly related to the occurrence of symptomatic intracranial hemorrhage (OR, 4.54; 95% CI, 1.83—11.23; OR, 6.12; 95% CI, 2.00—18.71).[18] Accordingly, it is important to maintain BP monitoring after IVT and maintain stable BP.

BP control in patients receiving EVT

BP control before EVT

The goal of BP control before EVT remains inconclusive. Mechanical Embolus Removal in Cerebral Ischemia (MERCI) found that patients with preoperative systolic BP greater than 150 mmHg were less likely to achieve successful reperfusion after thrombectomy.[19] The results of the BP analysis in the more recent Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial revealed a U-shaped relationship between systolic BP and functional prognosis. The best systolic BP was 120 mmHg.[20] However, preoperative BP is easily affected by the patient's previous BP, cerebral autoregulation, compensatory system, and thrombus burden that blocks the blood vessel[21] and is not a single factor that directly affects the prognosis after EVT. Recently, five of the six pivotal EVT clinical trials (REVASCAT, SWIFT PRIME, EXTEND-IA, THRACE, and MR CLEAN) and DAWN trials included preoperative BP greater than 185/110 mmHg as an exclusion criterion, based on the previous IVT treatment guidelines. Before clearer evidence supporting other BP control goals is obtained, it should be reasonable to adopt BP control goals for IVT.

Table 3 Proposed BP targets in different stages of IVT.

	BP target	References
Before IVT	<185/110 mmHg	Ref. 8
After IVT	<180/105 mmHg	Ref. 8, 16

BP control when receiving EVT

In 2014, the Society of Neurointerventional Surgery and the Neurocritical Care Society jointly published a consensus statement on anesthesia for ischemic stroke receiving intra-arterial therapy. The guidelines recommend to continuously monitor BP at 3-min intervals during the surgery, maintain systolic BP between 140 mmHg and 180 mmHg, and control diastolic BP to within 105 mmHg.[22]

In recent years, studies comparing the use of general anesthesia or conscious sedation for EVT have found that the BP-lowering effect of general anesthesia is related to poor prognosis. Therefore, many recent observational studies have explored intraoperative BP regulation in EVT. A retrospective case—control study of 108 patients with ischemic stroke undergoing EVT under general anesthesia indicated that a 40% decrease in intraoperative mean arterial BP (MAP) was an independent risk factor for poor prognosis (mRS>2) (OR, 2.8; 95% CI, 1.09—7.19).[23] Another retrospective case—control study that included 256 patients with ischemic stroke who received EVT with conscious sedation and achieved successful reperfusion showed that a reduction of >10% in MAP during EVT was associated with a poor prognosis (OR, 4.38; 95% CI, 1.53—12.56). When the MAP was under 100 mmHg, the OR of the poor prognosis in the patient with a decrease of 10 mmHg was 1.28 (95% CI, 1.01—1.62).[24] A case—control study including 390 patients with acute ischemic stroke undergoing EVT showed that, before the obstructed large blood vessels were opened, the extent of BP drop affected the prognosis; the ORs for a 10-mmHg decrease in MAP at discharge and for a 3-month difference in mRS (one step up in score) were 1.22 (95% CI, 1.12—1.34) and 1.17 (95% CI, 1.10—1.25), respectively.[25] A systematic review found that, once the intraoperative systolic BP was closely monitored and controlled between 140 mmHg and 180 mmHg, the aforementioned correlation between BP and prognosis no longer existed.[26] A recently published meta-analysis combined BP data and other clinical data from three clinical trials comparing general anesthesia and conscious sedation (SIESTA, ANSTROKE, and GOLIATH) and included 365 patients with anterior circulation ischemic stroke undergoing EVT. This study found that the presence of a continuous-episode intraoperative MAP of less than 70 mmHg for a minimum of 20 min (adjusted OR 2.30, 95% CI: 1.11—4.75) or intraoperative MAP greater than 90 mmHg for a minimum of 115 min (adjusted OR 1.89, 95% CI: 1.01—3.54) was associated with poorer 90-day mRS (per level of increase). The numbers needed to harm both were four and six, respectively.[27]

In summary, the monitoring and regulation of BP during EVT are extremely important, and a drastic BP drop should be avoided before successful reperfusion is achieved.

BP control after EVT

To date, no strong evidence supports a specific BP target value after EVT. In a 2017 single-center case–control study including 217 patients with ischemic stroke undergoing EVT, Goyal et al. found that every 10 mmHg increase in peak systolic BP at 24 h postoperatively predicted a lower 3-month chance of functional independence (mRS 0–2) (OR, 0.70; 95% CI, 0.56–0.87) and a higher 3-month mortality (OR, 1.49; 95% CI, 1.18–1.88).[28] Another two-center case–control study that included 690 patients with ischemic stroke who had undergone EVT analyzed BP within 24 h postoperatively and found that patients with good 3-month prognoses (mRS 0–2) had lower median systolic BPs (131 vs. 140 mmHg, $p < 0.0001$) than those with a poor 3-month prognosis (mRS>2). The median diastolic BP was a significant predictor of a good 3-month prognosis (OR, 0.98; 95% CI, 0.96–0.98). There was no significant correlation between symptomatic intracranial hemorrhage and BP.[29] Another multicenter prospective cohort study of 485 patients with ischemic stroke undergoing EVT (Blood Pressure after Endovascular Therapy for Ischemic Stroke [BEST]) analyzed BP within 24 h after EVT and found that peak systolic BP greater than 158 mmHg was significantly associated with a poor 90-day prognosis (mRS>2) (OR, 2.24; 95% CI, 1.52–3.29). Unfortunately, this statistical significance disappeared after adjusting for other factors (age, basic NIHSS, blood glucose level, reperfusion time, reperfusion degree, and BP at hospitalization).[30] A recently published meta-analysis including 6474 patients with acute ischemic stroke receiving EVT showed that increasing postoperative mean systolic BP levels were associated with lower odds of 3-month functional independence after adjusting for all potential confounders (OR, 0.80; 95% CI, 0.72–0.89).[31] However, none of the abovementioned studies considered the postoperative recanalization status.

Recanalization of blood vessels after EVT

In contrast to the fact that the status of vascular recanalization cannot be directly identified after IVT, EVT interventionalists can obtain a clear picture of postoperative vascular patency and perfusion. If successful reperfusion is achieved after EVT, high BP may cause reperfusion injury and cerebral hemorrhage. However, if the blood vessel remains obstructed after the surgery, BP lowering may further aggravate the hypoperfusion situation.[21] Therefore, vascular patency must be considered in the discussion of postoperative BP control.

In reviewing past clinical trials, the DAWN trial protocol for successful reperfusion cases (TICI 2b-3) suggested to maintain the systolic BP below 140 mmHg within 24 h after EVT.[32] However, there is no reliable evidence to support this goal. The abovementioned study conducted by Goyal et al., in 2017 further divided 145 of 217 cases that achieved successful reperfusion into intensive BP goal (<140/90 mmHg), moderate BP goal (<160/90 mmHg), and permissive hypertension (<220/110 mmHg, if combined with IVT, it should be reduced to 180/105 mmHg). The group with moderate BP goal had lower 3-month mortality (OR, 0.08; 95% CI, 0.01–0.54) relative to the group with permissive hypertension, whereas the group with intensive BP goal had too few cases ($N = 10$) to be conclusive.[28] In addition, several small-scale retrospective studies showed that cases of successful reperfusion after EVT with lower and more stable BP within 24 h had a better prognosis. A recent multicenter retrospective cohort study analyzed 1019 cases of ischemic stroke after successful reperfusion (mTICI 2b-3) following EVT. The authors divided all patients into three groups according to the systolic BP treatment goals for 24 h after surgery: <140 mmHg, <160 mmHg and <180 mmHg. The results showed that compared to controlling the systolic BP < 180 mmHg, controlling the systolic BP below 140 mmHg had a better 90-day functional prognosis (OR, 1.53; 95% CI, 1.07–2.19) and a lower chance of requiring craniotomy (OR, 0.18; 95% CI, 0.16–0.21). Controlling the systolic BP to within 160 mmHg significantly reduced the 90-day mortality rate compared with systolic BP controlled to within 180 mmHg (OR, 0.42; 95% CI, 0.22–0.82).[33] Moreover, a case–control study of 166 cases of ischemic stroke who had received EVT to achieve successful reperfusion showed that, under the condition of setting the postoperative systolic BP control target at less than 140 mmHg, the BP value within 24 h after surgery was significantly related to the 3-month functional prognosis. Among them, the BP within 6 h after surgery was the most important. Systolic BP (OR, 0.96; 95% CI, 0.93–0.99) and peak diastolic BP (OR, 0.94; 95% CI, 0.91–0.98) within 6 h after surgery significantly predicted the 3-month functional prognosis (mRS 0–2). This demonstrates the importance of immediate BP control after EVT.[34] However, the abovementioned results were all based on retrospective observational studies that were non-randomized and can only be used as a reference in subsequent larger-scale clinical trials.

In summary, for cases with successful reperfusion after EVT, BP can be controlled in a lower range within 24 h or even 6 h postoperatively (i.e., control of BP to <140/90 mmHg according to the DAWN trial).

Table 4 listed the proposed BP targets for different stages of EVT.

In addition to the absolute value of BP, fluctuations in BP are also reportedly related to the prognosis after EVT. In a case–control study of 182 patients with ischemic stroke who had undergone EVT, the systolic BP SV within 24 h after surgery significantly predicted a 3-month increase (worse function) in the mRS score (OR, 2.63; 95% CI, 1.47–4.70).[35] The follow-up analysis of the above BEST trial also showed that higher BP fluctuations were associated with a poor 90-

Table 4 Proposed BP targets in different stages of EVT.

	BP target	References
Before EVT	<185/110 mmHg	Ref. 8
During EVT	Avoid drastic BP fluctuation	Ref. 23–27
After EVT (mTICI 0-2a)	<180/105 mmHg	Ref. 28–34
After EVT (mTICI 2b-3)	<140/90 mmHg	Ref. 28–34

day prognosis. Therefore, it is important to continuously monitor and control BP after EVT.[36]

Rather than using the same standard BP treatment goal for every patient, some scholars believe that individual BP control goals should be based on cerebral autoregulation. A prospective cohort study enrolling 90 patients with anterior circulation ischemic stroke undergoing EVT was designed to identify individualized autoregulation-based upper and lower BP limits by measuring the cerebral blood flow and BP with a near-infrared spectrometer. The percentage of time that the MAP exceeded the autoregulation-based upper limit within 12 h after EVT significantly correlated with the 90-day prognosis (OR, 1.84 per 10% of the time exceeding the upper limit of BP; 95% CI, 1.30—2.70). However, correlation with the absolute BP was not significant.[37]

Currently, EVT is the standard treatment for ischemic stroke with large-vessel occlusion. Postoperative BP control requires a large-scale randomized controlled trial to provide better evidence to support clinical decision making.

Recommended antihypertensive drugs

The choice of antihypertensive drug is inconclusive. A review of 26 studies in 2014 observed no evidence to support the routine use of certain classes of antihypertensive drugs acute-phase stroke.[38] Generally speaking, the use of intravenous short-acting drugs in the acute phase is recommended to quickly exert the effects and prevent long-term drug effects that may lead to excessively low BP.[21] The antihypertensive drugs commonly used in the acute phase are listed in Table 5.

Recommendations for BP control in the acute phase of ischemic stroke

1. For those who have not received reperfusion therapy, it is recommended not to start antihypertensive drugs unless the systolic BP exceeds 220 mmHg or the diastolic BP exceeds 120 mmHg within 24 h of an ischemic stroke, except for situations that require emergency BP reduction (such as severe heart failure, aortic dissection, and hypertensive encephalopathy). It is also recommended to control the initial systolic BP drop to less than 15% and closely monitor for neurological deficits (COR, I; LOE, C-EO).
2. For those eligible for IVT, it is recommended to control BP to under 185/110 mmHg before injection (COR, I; LOE, C-EO).
3. Within 24 h after receiving IVT, it is recommended to control BP to under 180/105 mmHg (COR, I; LOE, B-NR).
4. For those eligible for EVT, it is reasonable to control BP to under 185/110 mmHg before the procedure if IVT is not performed (COR: IIa, LOE: B-NR).
5. For patients receiving EVT, it is recommended that BP values be continuously and closely monitored during the procedure (COR: I, LOE: C-EO).
6. For patients undergoing EVT, it is reasonable to avoid a decrease in the mean arterial BP by over 40% before successful reperfusion is achieved (COR: IIa, LOE: B-NR).
7. For patients undergoing EVT, if the mean arterial BP cannot be obtained during the procedure, it is reasonable to control the systolic BP between 140 mmHg and 180 mmHg (COR: IIa, LOE: C-EO).
8. For patients receiving EVT, it is reasonable to maintain the BP at less than 180/105 mmHg within 24 h after the procedure (COR: IIa, LOE: B-NR). If successful

Table 5 Commonly used antihypertensive drugs in acute phase.

Drug	Dosage and usage	Route of administration	Onset start time (min)	Duration of efficacy	Precautions
Labetalol	10—20 mg IV over 1—2 min	IV bolus, infusion	2—5	2—4 h	Pay attention to bradycardia and avoid using it in patients with high degree AV block
Nicardipine	5 mg/h IV, uptitrate 2.5 mg/h every 5—15 m, max: 15 mg/h	IV infusion	5—15	4—6 h	Not for use in patients with severe aortic stenosis
Hydralazine	10—20 mg IV, repeat every 4—6 h prn, max: 40 mg	IV bolus	10—20	~12 h	Pay attention to tachycardia, intracranial hypertension (used as a later-line)
Enalaprilat	0.625—1.250 mg IV every 6 h	IV bolus	<15	~6 h	It should not be used for patients with bilateral renal artery stenosis, pay attention to the angioedema caused by ACEI
Sodium Nitroprusside	0.3—0.5 mcg/kg/min	IV infusion	1—2	2—3 min	Pay attention to intracranial hypertension (used as later-line)
Glyceryl Trinitrate	5 mg/day	Transdermal	30—60	12—14 h	Pay attention to allergies. Cannot be used in combination with phosphodiesterase-5 inhibitor

reperfusion (mTICI 2b-3) is achieved, maintaining BP at a lower value (such as <140/90 mmHg) within 24 h after the procedure can be considered (COR: IIb, LOE: B-NR).

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Conflict of interest

The authors declare no conflict of interest.

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