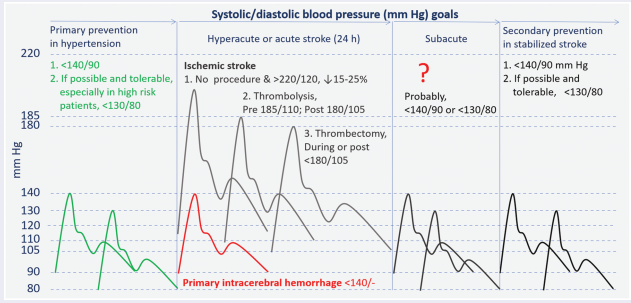
Blood Pressure Goals in Acute Stroke

Qian-Hui Guo,[1] Chu-Hao Liu,[1] and Ji-Guang Wang[1,]

Antihypertensive treatment is highly effective in both primary and secondary prevention of stroke. However, current guideline recommendations on the blood pressure goals in acute stroke are clinically empirical and generally conservative. Antihypertensive treatment is only recommended for severe hypertension. Several recent observational studies showed that the relationship between blood pressure and unfavorable clinical outcomes was probably positive in acute hemorrhagic stroke but J- or U-shaped in acute ischemic stroke with undetermined nadir blood pressure. The results of randomized controlled trials are promising for blood pressure management in hemorrhagic stroke but less so in ischemic stroke. A systolic blood pressure goal of 140 mm Hg is probably appropriate for acute hemorrhagic stroke. The blood pressure goal in acute ischemic stroke, however, is uncertain, and probably depends on the time window of treatment and the use of revascularization therapy. Further research is required to investigate the potential benefit of antihypertensive treatment in acute stroke, especially with regard to the possible reduction of blood pressure variability and more intensive blood pressure lowering in the acute and subacute phases of a stroke, respectively.

GRAPHICAL ABSTRACT



Keywords: acute stroke; blood pressure; blood pressure goals; guidelines; hypertension; observational studies; randomized controlled trials.

https://doi.org/10.1093/ajh/hpac039

Hypertension remains the most powerful risk factor of stroke worldwide[1] and in the stroke prone population in Asia,[2] irrespective of its subtype, either hemorrhagic or ischemic.[1,2] Antihypertensive drug treatment is highly effective in primary prevention of stroke in patients with hypertension.[3,4] Current hypertension guidelines recommend initiation of antihypertensive drug treatment in patients with conventionally defined hypertension (systolic/diastolic blood pressure ≥ 140/90 mm Hg)[5–8] and in high-risk patients with hypertension newly defined in the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (≥130/80 mm Hg).[9] In most guidelines, blood pressure is recommended to reduce to a level below 140/90 mm Hg and if possible and tolerable to 130/80 mm Hg or even lower.[5–8] The ACC/AHA guidelines recommend a universal blood pressure goal of 130/80 mm Hg.[9] In fact, the relationship between blood pressure and the risk of stroke is linear and direct, regardless whether blood pressure is measured in the office[10] or out-of-office setting.[11] In addition, the benefit of antihypertensive drug treatment is greater for the prevention of stroke than for other clinical outcomes, such as coronary events.[3,4] Indeed, the relative risk reduction for approximately each 10/5 mm Hg reduction in systolic/diastolic blood pressure was about 42% for stroke and 14% for coronary events in patients with systolic and diastolic hypertension.[3] The corresponding risk reductions in patients with isolated systolic hypertension were 30% and 23%, respectively.[4] No J-curve has ever been observed for stroke,[12] as for other clinical outcomes such as coronary events.[13,14]

In patients with a history of cerebrovascular disease, antihypertensive drug treatment is still highly effective in the prevention of recurrent stroke.[15] In the China

Correspondence: Ji-Guang Wang (jiguangwang@rjh.com.cn).
Initially submitted March 12, 2022; date of first revision March 17, 2022; accepted for publication March 19, 2022; online publication March 22, 2022.

[1]Department of Cardiovascular Medicine, State Key Laboratory of Medical Genomics, Shanghai Key Laboratory of Hypertension, Centre for Epidemiological Studies and Clinical Trials, The Shanghai Institute of Hypertension, National Research Centre for Translational Medicine at Shanghai, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

Post-stroke Antihypertensive Treatment (PATS) trial in patients with a stabilized stroke, antihypertensive drug treatment with a thiazide-like diuretic indapamide 2.5 mg per day reduced systolic/diastolic blood pressure by 5/2 mm Hg and the incidence of recurrent stroke by 29%.[16,17] The multinational Perindopril Protection Against Stroke Recurrence Study (PROGRESS) confirmed the beneficial effects of antihypertensive drug treatment in the prevention of recurrent stroke in patients with a stabilized recent cerebrovascular disease.[18] Antihypertensive drug treatment with either perindopril alone (4 mg per day) or perindopril and indapamide combination reduced systolic/diastolic blood pressure by 9/4 mm Hg and the incidence of recurrent stroke by 28%.[18] When these 2 trials were combined with four other antihypertensive treatment trials in patients with a history of cerebrovascular disease, the overall reduction in the risk of recurrent stroke was 25%,[15] with approximately a mean reduction of 7/3 mm Hg in systolic/diastolic blood pressure.[19]

Several subsequent trials included both patients with a stabilized recent stroke and those with an acute stroke, and showed modest or no benefit of blood pressure lowering.[20,21] In the Prevention Regimen for Effectively Avoiding Secondary Strokes (PRoFESS) trial in 20,332 patients with a recent ischemic stroke (median interval from stroke to randomization 15 days), telmisartan 80 mg per day reduced systolic/diastolic blood pressure by 3.8/2.0 mm Hg during a mean follow-up of 2.5 years.[20] The risk reduction in recurrent stroke was only 5% and statistically non-significant ($P = 0.23$).[20] In the Secondary Prevention of Small Subcortical Strokes (SPS3) trial in 3020 patients with a recent lacunar stroke (median time from qualifying stroke to randomization 62 days), systolic blood pressure lowering with a lower target (<130 mm Hg), compared with higher-target (130–149 mm Hg), reduced systolic blood pressure from 138 mm Hg to 127 mm Hg by 11 mm Hg during a mean follow-up of 3.7 years.[21] The risk reduction in the lower than higher target group was non-significant for all recurrent stroke (hazard ratio 0·81, $P = 0·08$), but significant for intracerebral hemorrhage (hazard ratio 0·37, $P = 0·03$).[21]

In the acute phase of a stroke, blood pressure management is apparently much more complex than for primary prevention of stroke in patients with hypertension or for secondary prevention in patients with a stabilized stroke. A key question is at what level of blood pressure do we need to initiate antihypertensive treatment and how low may we reduce blood pressure. A similarly important but even more difficult question is at what time after a stroke do we need to initiate antihypertensive treatment. In the past 2 decades, a number of observational studies and randomized clinical trials addressed these questions in patients with various subtypes of stroke. In the present review article, we first summarize the current guideline recommendations in this particular regard, and then the recent observational and clinical trial evidence on the blood pressure goals in acute stroke.

SEARCH STRATEGY AND SELECTION OF PUBLICATIONS

A total of 12,464 abstracts and full-text articles were systematically retrieved from electronic databases (PubMed and Embase) and manual search on January 28, 2022. For the search from electronic databases, we used terms: "blood pressure", "acute", "stroke", "intracerebral hemorrhage", "brain hemorrhage", and "cerebral hemorrhage". We also searched manually from the reference lists of identified articles.

Eligible studies were published in full-text articles in English, which presented data from prospective or retrospective observational studies or randomized clinical trials. To be eligible for inclusion, an observational study should have investigated the relationship between blood pressure measured within 14 days of an acute stroke and clinical outcomes, and a randomized clinical trial should have compared various goals of blood pressure control or various intensities of antihypertensive treatment. We also searched and reviewed current guidelines for the blood pressure management in acute stroke. Finally, we presented in this review 5 guidelines,[22–26] 33 observational studies,[27–59] and 12 randomized clinical trials (Figure 1).[60–71]

CURRENT GUIDELINE RECOMMENDATIONS

In addition to the European Stroke Organization guidelines on blood pressure management in acute ischemic and hemorrhagic stroke,[22] several recent stroke-specific guidelines also provide detailed recommendations on blood pressure management in the acute phase of hemorrhagic[23,24] and ischemic stroke (Table 1).[25,26] The recommendations for hemorrhagic stroke are straightforward and consistent between various guidelines.[22–24] The recommendations for ischemic stroke, however, are complicated, not only because of weak evidence, but also because of the complexity in the treatment, such as the use of intravenous thrombolysis and more recently arterial mechanical thrombectomy.[22,25,26]

The recent guideline recommendations for blood pressure management in acute hemorrhagic stroke were heavily influenced by the results of the intensive blood pressure reduction in an acute intracerebral hemorrhage trial (INETERACT), which is the largest ever blood pressure lowering trial in acute intracerebral hemorrhage.[61] Although the benefit of intensive blood pressure lowering to a level of 140 mm Hg systolic was only borderline significant, it provided evidence that early intensive blood pressure was safe and probably beneficial in functional recovery in those patients with acute hemorrhagic stroke and systolic blood pressure of 150–220 mm Hg.[61] The AHA/American Stroke Association (ASA) guidelines substantially simplified the recommendations that in patients with a systolic blood pressure of 150–220 mm Hg and without contraindication to acute blood pressure treatment acute systolic blood pressure lowering to 140 mm Hg is safe and can be effective for improving functional outcome.[23] This AHA/ASA guidelines continued to recommend aggressive blood pressure reduction with a continuous intravenous infusion and frequent blood pressure monitoring in those patients with a systolic blood pressure of $\geq$ 220 mm Hg. The subsequent Canadian[24] and European[22] guidelines provided similar recommendations.

The complexity of blood pressure management in acute ischemic stroke is mainly related to the use of

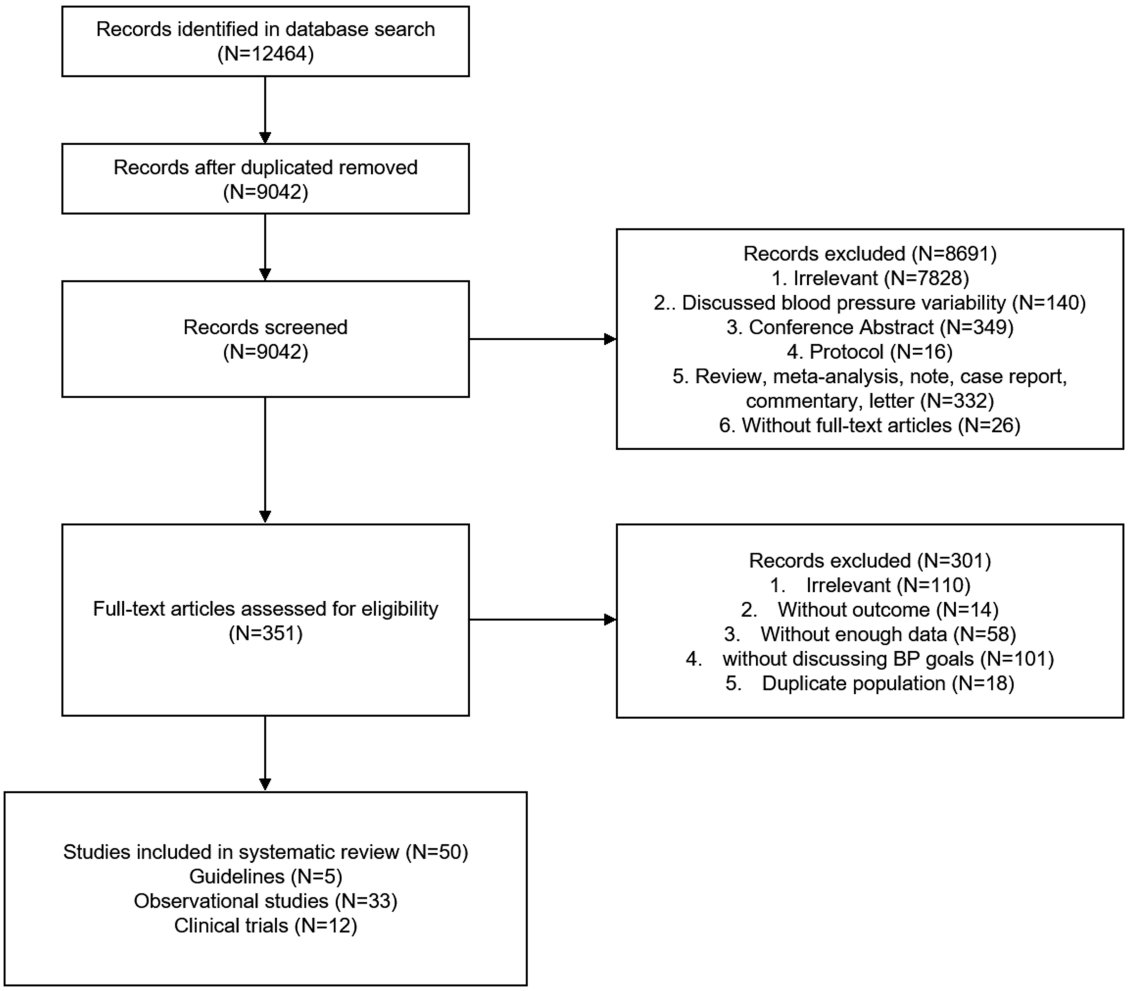


Figure 1. Flow diagram of selection procedure for studies.

intravenous thrombolytic therapy and arterial mechanical thrombectomy. In general, the current guidelines are conservative in recommending blood pressure lowering treatment in acute ischemic stroke unless systolic/diastolic blood pressure is extremely high, e.g., >220/120 mm Hg.[22,25,26] However, the current guidelines recommend that systolic/diastolic blood pressure should be reduced to and maintained at a level below 185/110 mm Hg and 180/105 mm Hg in those patients who undergo treatment with intravenous thrombolytic therapy and arterial mechanical thrombectomy, respectively.[22,25,26]

In addition to the guidelines specifically for various subtypes of strokes,[22–26] current hypertension guidelines also provide recommendations for blood pressure management in acute hemorrhagic and ischemic stroke.[5,7,9] The recommendations of these hypertension guidelines are generally conservative in blood pressure management in acute intracerebral hemorrhage as well as acute ischemic stroke. For instance, these guidelines do not recommend immediate blood pressure lowering in patients with a hemorrhagic stroke and a systolic blood pressure of 150–220 mm Hg, because of safety concerns on renal outcomes in the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-2 trial.[62,7] However, these guidelines do recommend timely start or restart of antihypertensive drug treatment for secondary prevention.[7,9] The European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines recommend that for stable patients who remain hypertensive (≥140/90 mm Hg) more than 3 days after an acute ischemic stroke, initiation, or reintroduction of blood pressure-lowering medication should be considered.[7]

OBSERVATIONAL EVIDENCE

A number of observational studies investigated the association between blood pressure at various timepoints after a stroke and short- and long-term clinical outcomes (Table 2).[27–59] These studies focused on the level of blood pressure at admission or in the initial hours or days of hospitalization. Most of these studies investigated systolic and diastolic components of blood pressure. Some studies also included mean arterial pressure and pulse pressure. However, there was no standardized protocol for blood pressure measurement in the early critical phase of a stroke.

Table 1. Current guideline recommendations on blood pressure goals in acute stroke

	Recommendations on blood pressure management	
Guideline	**Clinical situation**	**Blood pressure lowering and monitoring**
Hemorrhagic stroke		
AHA/ASA 2015[23]	SBP 150–220 mm Hg and without contraindication to acute BP treatment	Acute lowering of SBP to 140 mmHg is safe and can be effective for improving functional outcome.
	SBP > 220 mm Hg	It may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring.
Canadian 2020[24]		A SBP threshold at an individual target of < 140–160 mm Hg for the first 24–48 hours post stroke onset may be reasonable.
ESO 2021[22]	Hyperacute (<6 hours) intracerebral hemorrhage	SBP < 140 mm Hg (and > 110 mm Hg) to reduce hematoma expansion
Ischemic stroke		
AHA/ASA 2018[25]	Patients who have elevated BP and are otherwise eligible for treatment with intravenous alteplase	SBP/DBP < 185/110 mm Hg before intravenous fibrinolytic therapy
	Patients for whom intra-arterial therapy is planned and who have not received intravenous thrombolytic therapy	It is reasonable to maintain SBP/DBP ≤ 185/110 mm Hg before the procedure.
Canadian 2018[26]	Eligible for thrombolytic therapy and SBP/DBP > 185/110 mm Hg	<185/110 prior to alteplase therapy and < 180/105 mm Hg for the next 24 hour after alteplase administration
	SBP/DBP > 220/120 mm Hg	Reduce BP by ~15%, and not > 25%, over the first 24 hours with further gradual reduction thereafter to targets for long-term secondary stroke prevention
ESO 2021[22]	SBP/DBP < 220/110 mm Hg and not treated with intravenous thrombolysis or mechanical thrombectomy	No routine use of BP lowering agents at least in first 24 hours following symptom onset, unless necessary for a specific comorbid condition
	Undergoing treatment with intravenous thrombolysis (with or without mechanical thrombectomy)	SBP/DBP < 185/110 mm Hg before bolus and below 180/105 mm Hg after bolus, and for 24 hours after alteplase infusion
	Large vessel occlusion undergoing mechanical thrombectomy (with or without intravenous thrombolysis)	SBP/DBP < 180/105 mm Hg during and 24 hours after mechanical thrombectomy

Guidelines are listed in the ascending order of the year of publication for hemorrhagic and ischemic stroke separately.

Abbreviations: AHA/ASA, American Heart Association/American Stroke Association; BP, blood pressure, DBP, diastolic blood pressure; ESO, European Stroke Organization; SBP, systolic blood pressure.

Table 2. Observational studies on the relationship between blood pressure and clinical outcomes in acute hemorrhagic and ischemic stroke since 2002

First author and year of publication	Design	Time window[a]	No. of Patients	Men (%)	Age, years	Baseline SBP/DBP, mm Hg	Anti-HT (%)	Primary outcome	Major findings on blood pressure goals
Hemorrhagic stroke									
Koga, 2012[27]	PP	3 h	211	62	66	202/108	NA	Neurological deterioration within 72 h (GCS decrement ≥ 2 points or NIHSS increment ≥ 4 points) and SAE to stop IV nicardipine within 24 h	Treating to SBP ≤ 160 mm Hg was safe and feasible.
Sakamoto, 2013[28]	PP	3 h	211	62	65	200/80	NA	Neurological deterioration within 72 h (GCS decrement ≥ 2 or NIHSS increment ≥ 4), hematoma expansion > 33% from baseline to 24 h, and mRS 4–6 at 3 months	A mean achieved SBP ~130 mm Hg was associated with the lowest odds ratios for worse outcomes.
Rodriguez-Luna, 2014[29]	RT	6h	117	58	71	172/92	NA	Hematoma growth at 24 h, early neurological deterioration, 24 h and 90-day mortality, and poor outcome	SBP lowering to ≤ 160 mm Hg minimized the deleterious effect on 24 h outcomes.
Mustanoja, 2018[30]	RT	24h	334	61	40	155/92	51	3-month and long-term (median of 12 years) mortality	SBP ≥ 160 mm Hg had higher 3-month and long-term mortality.
Zhao, 2019[31]	RT	6 h	659	71	65	165/101	NA	Mortality, rates of operation, length of ICU stay, and mRS at 90 days	SBP < 140/90 mm Hg had smaller hematoma growth and lower rates of operation and mRS.
Francoeur, 2021[32]	RT	24 h	384	61	66	179/96	NA	Death or moderate-to-severe disability at 3 months (mRS 4–6)	SBP > 140 mm Hg had poor outcome.
Ischemic stroke without thrombolysis or mechanical thrombectomy									
Castillo, 2004[33]	PP	24 h	304	52	72	179/97	22.1	Early neurological deterioration at 48 h and neurological deficit and mortality at 90 days	U-shaped association with a nadir SBP/DBP at admission and 24 h 180/100 mm Hg; SBP/DBP ↓ >20 mm Hg within the first 24 h had poor prognosis.
Vemmos, 2004[34]	PP	24 h	1121	57	71	NA	NA	Mortality at 1 and 12 months	Patients with admission SBP > 220 mm Hg or < 120 mm Hg had higher mortality.
Abboud, 2006[35]	PP	24 h	230	64	67	150/84	NA	Mortality or dependency (mRS > 3) at 10 days and 6 months	SBP ≥ 165 mm Hg had poor outcome at 10 days and 6 months.
Sartori, 2006[36]	PP	24 h	71	77	76	160/86	22.4	Mortality at 3 months	MAP decrease > 5 mm Hg had better outcome.
Armario, 2008[37]	PP	3 h	100	51	74	163/88	2.0	Functional recovery (mRS ≤ 2) at discharge and 3 months	SBP ≥ 185 mm Hg had poor outcome at discharge and 3 months.
Weiss, 2013[38]	PP	24 h	177	50	84	151/78	51	Functional status (mRS) and mortality (≤5 years)	24 h mean SBP > 160 mm Hg was associated with higher mortality.
Hao, 2014[39]	PP	2–270 h[b]	215	60	60	142/84	40.5	Death or disability (mRS > 2) at 3 months	SBP/DBP 120–159/70–89 mm Hg had the lowest risk.

Table 2. Continued

First author and year of publication	Design	Time window[a]	No. of Patients	Men (%)	Age, years	Baseline SBP/DBP, mm Hg	Anti-HT (%)	Primary outcome	Major findings on blood pressure goals
Ishitsuka, 2014[40]	PP	24 h	1874	62	70	149/81	33.4	Neurological recovery (NIHSS decrement ≥ 4 in hospital or = 0 at discharge); early neurological deterioration (NIHSS increment ≥ 2 in hospital); death or disability (mRS > 2) at 3 months	SBP/DBP ≥ 144/89 mm Hg predicted poor outcome.
Wohlfahrt, 2015[41]	PP	24 h	532	59	66	NA	62	Mortality during a median follow-up of 66 weeks	All-cause mortality increased with admission MBP < 100 mm Hg and discharge SBP < 120 mm Hg.
Mustanoja, 2016[42]	PP	24 h	1004	63	44	141/86	36	Recurrent stroke during a median follow-up of 8.9 years	SBP/DBP ≥ 160/100 mm Hg had a higher risk of recurrent stroke.
Bangalore, 2017[43]	PP	4.5 h	309,611	48	74	NA	NA	In-hospital mortality, not discharged, inability to ambulate at discharge and hemorrhagic complications due to thrombolysis	U-shaped or J-shaped association with a nadir at 150/70 mm Hg
Kang, 2019[44]	RT	48 h	3723	59	67	134/-	NA	Unfavorable outcome (mRS > 2) at discharge and time to composite cardiovascular event of stroke, myocardial infarction, and vascular death for 1-year follow-up.	SBP > 156 mm Hg had worse outcome than SBP ≤ 133.2 mm Hg.
Ajinkya, 2020[45]	RT	24 h	1232	49	67	158/85	NA	Mortality and mRS ≤ 2 at 90 days	SBP ≤ 139–157 mm Hg in the tPA group and ≤ 137–181 mm Hg in the non-tPA group had a lower risk of 90-day mortality.
Ischemic stroke with thrombolysis and mechanical thrombectomy									
Intravenous thrombolysis									
Wu, 2017[46]	RT	Pre & post	383	73	61	148/-	44.6	Unfavorable outcome (mRS 3–6) at 3 months	Post thrombolysis SBP ≤ 160 mm Hg had a favorable outcome.
He, 2021[47]	RT	Pre, post, 24 h, & 7 d	510	65	65	158/90	42.6	mRS ↓ ≥2 points or 0–3 at 3 months	SBP < 148 mm Hg in the first 24 h after thrombolysis then SBP 127–138 mm Hg would be beneficial.
Mechanical thrombectomy									
Goyal, 2017[48]	PP	24 h post	217	50	62	158/90	19.8	Functional recovery (mRS 0–2) at 3 months	SBP/DBP < 160/90 mm Hg during the first 24 h after MT was associated with a lower risk of 3-month mortality.
Maïer, 2017[49]	PP	12 h	1042	54	68	149/81	NA	All-cause mortality, good outcome (mRS of 0–2) at 3 months, and ICH	Baseline SBP ≥ 177 mm Hg predicted unfavorable outcome.
Anadani, 2019[50]	PP	24 h post	298	49	67	146/-	61.4	Mortality and unfavorable outcome (mRS > 2) at 3 months	SBP < 120 mm Hg at 24 h after MT had a better 90-day outcome and lower mortality.

Table 2. Continued

First author and year of publication	Design	Time window[a]	No. of Patients	Men (%)	Age, years	Baseline SBP/DBP, mm Hg	Anti-HT (%)	Primary outcome	Major findings on blood pressure goals
Anadani, 2019[51]	RT	24 h post	1245	51	69	144/80	NA	90-day mRS, symptomatic ICH, mortality, and hemicraniectomy	High blood pressure with higher risk.
van den Berg, 2020[52]	PP	6.5 h	3180	48	72	150/82	54	Mortality and unfavorable outcome (mRS > 2) at 3 months	J-shaped association with a nadir at 150/81 mm Hg of admission SBP/DBP
An, 2021[53]	RT	24 h post	164	68	65	146/80	NA	ICH during the first 24 h after MT	Optimal maximum SBP/DBP ≤ 155/92.5 mm Hg
Chen, 2021[54]	PP	Admission, pre, & post	139	41	76	169/93	NA	Favorable outcome (mRS 0–3) at 3 months	Admission SBP ≤ 187 mm Hg and MAP ≤ 125 mm Hg; Pre-MT SBP ≤ 163 mm Hg; and MAP ≤ 117 mm Hg
Gigliotti, 2021[55]	RT	24 h post	117	47	65	NA	27.3	mRS at discharge and 3 months, incidence of ICH, malignant cerebral edema, hemicraniectomy, mortality at 3 months, and discharge disposition	SBP ≥ 180 mm Hg predicted poor functional outcome at discharge. SBP ≥ 160 mm Hg resulted in an increased odds of malignant cerebral edema.
Intravenous thrombolysis or mechanical thrombectomy									
Choi, 2019[56]	PP	72 h	1540	56	69	130/82	NA	mRS 0–2 at 3 months	SBP/DBP ≤ 130/80 mm Hg was associated with favorable outcome.
Mixed (hemorrhagic/ischemic) stroke									
Okumura, 2005[57]	PP	24 h	1097/1004/	53/56	64/70	182/99 162/88	NA	Mortality at 30 days	For ICH, SBP/DBP ≥ 230/120 mm Hg higher mortality; For AIS, U-shaped association with a nadir at 150–169/110–110 mm Hg.
Zhang, 2008[58]	RT	24 h	1760/2178	60/62	56/61	172/104 152/92	NA	Death and disability/dependence during hospitalization	For ICH, ≥140 mm Hg, higher risk; For AIS, no association.
Furlan, 2018[59]	RT	48 h	45/101	53/55	64/68	173/79 156/91	NA	All-cause mortality during the first 7 days	For ICH, no association; For AIS, SBP ≤ 131 mm Hg, higher mortality.

Studies are listed in the order of the year of publication with each subsection.

Abbreviations: AIS, acute ischemic stroke; Anti-HT, anti-hypertensive agents; BP, blood pressure; DBP, diastolic blood pressure; END, Early Neurological Deterioration; ICH, intracerebral hemorrhage; ICU, intensive care unit; IV, intravenous; MAP, mean arterial pressure; mRS, modified Rankin Scale; MT, mechanical thrombectomy; mTICI, modified Treatment in Cerebral Ischemia; NA, not available; NIHSS, National Institutes of Health Stroke Scale; PP, prospective; RT, retrospective; SBP, systolic blood pressure; tPA, tissue plasminogen activator.

[a]Time windows refers to time from the onset of stroke to admission.

[b]Patients with severe intracranial stenosis or occlusion.

Hemorrhagic Stroke

Our literature search identified one prospective observational study with 2 publications[27,28] and 4 retrospective analysis reports.[29–32] The only prospective study required that patients had an entry systolic blood pressure of at least 180 mm Hg. The mean baseline systolic and diastolic blood pressure in this prospective study was 202/108 mm Hg and much higher than that in the retrospective studies without any entry criteria of blood pressure (from 155/92 mm Hg[30] to 179/96 mm Hg).[32] The prospective study showed that treating systolic blood pressure to a level below 160 mm Hg was safe and feasible. In a post-hoc analysis of this prospective study, the investigators further analyzed the relationship between achieved systolic blood pressure and clinical outcomes, and found that an approximately 130 mm Hg of the achieved systolic blood pressure was associated with the lowest odds ratio for worse clinical outcomes. The retrospective analyses consistently showed that a lower systolic blood pressure below 160 mm Hg[29,30] or 140 mm Hg[31,32] was associated with better clinical outcomes.

Ischemic Stroke

The number of observational studies for acute ischemic stroke[33–59] was much greater than for acute hemorrhagic stroke.[27–32] These studies were mostly prospectively designed and dealt with 2 different situations of treatment, i.e., without or with intravenous thrombolysis and arterial mechanical thrombectomy.

In the absence of the interventional revascularization therapy, J- or U-shaped relationship between blood pressure and clinical outcomes after an acute ischemic stroke was observed in almost all studies,[33–45] including the US Get With The Guidelines-Stroke registry with a huge number of patients (n = 309,611).[43] Both high and low blood pressures at admission and the initial hours after an acute ischemic stroke were associated with unfavorable clinical outcomes. However, the nadir was different between these studies from 120 to 185 mm Hg of systolic blood pressure, but mostly around 150–160 mm Hg. The difference might have been influenced by several factors. Among others, the timepoint of blood pressure measurement might be crucial. The nadir was higher in the analysis on admission blood pressure than mean blood pressure during the first 24- or 48-hours after stroke onset. There was often a spontaneous blood pressure decline after admission even without any blood pressure lowering medication.

With the shortening of the time from door to needle and the technological advancing, there is an increasing proportion of patients who receive either intravenous thrombolysis or arterial mechanical thrombectomy. Under the circumstances of these interventions, the relationship between blood pressure and clinical outcomes after an acute ischemic stroke is becoming even more complicated. Blood pressure can be measured at admission and pre- or post-procedure. Two retrospective studies consistently showed that patients with a lower post-thrombolysis systolic blood pressure had favorable clinical outcomes with a nadir at 160[46] and 148 mm Hg,[47] respectively.

The prognostic significance of blood pressure in patients receiving arterial mechanical thrombectomy was investigated in several prospective[48–50,52,54] and retrospective studies.[51,53,55] These studies were consistent in showing that lower blood pressure was associated with better clinical outcomes. However, the timepoint of blood pressure measurement again was an issue, including admission, pre-procedure, and hours and days post-procedure. How low a blood pressure was associated with a favorable outcome is also an issue. When admission blood pressure was considered, the threshold was approximately 160–180 mm Hg. When post-thrombectomy blood pressure was considered, it was about 20 mm Hg lower, down to 120 mm Hg. The procedure probably increases the likelihood of benefit from blood pressure lowering in patients with an acute ischemic stroke. Indeed, a blood pressure below 130 mm Hg systolic and 80 mm Hg diastolic was associated with favorable clinical outcomes in a study in patients treated with intravenous thrombolysis or mechanical thrombectomy and with blood pressure data collected within 72 hours of an acute ischemic stroke.[56]

Mixed Hemorrhagic and Ischemic Stroke

Three studies included both patients with acute intracerebral hemorrhage and those with acute ischemic stroke.[57–59] These studies allowed comparison between these 2 subtypes of stroke with regard to the relationship between blood pressure and clinical outcomes. Higher blood pressure was associated with a higher risk of unfavorable clinical outcomes in patients with hemorrhagic stroke in 2 of the 3 studies.[57,58] A J-shaped association was observed in patients with acute ischemic stroke in 2 of the 3 studies.[57,59] Again, the nadir was different between these studies for both hemorrhagic and ischemic stroke, similarly as the abovementioned studies.

CLINICAL TRIAL EVIDENCE

Observational studies provided useful evidence for blood pressure management in acute stroke. However, the findings are generally hypothesis-generating and need to be confirmed in randomized controlled trials. In the past 2 decades, several trials have been conducted to test whether blood pressure lowering is beneficial in the prevention of mortality and dependency in acute hemorrhagic[60–63] or ischemic stroke[64–67] or both (Table 3).[68–71] Most of these randomized antihypertensive treatment trials in acute stroke were with a clearly defined goal of blood pressure lowering.[60–67,69,71] Usually, any antihypertensive treatment could be used to achieve the goal of blood pressure control. Two studies, however, were without a goal of blood pressure lowering but with a standardized antihypertensive treatment regimen.[68,70] Although a trial with the latter design does not have a priori hypothesis of blood pressure targets, the achieved blood pressure during treatment also provides guidance on blood pressure goals.

Table 3. Antihypertensive treatment trials in acute stroke

First author and year of publication	Time window[a]	No. of patients	Men (%)	Mean age at baseline, years	Mean SBP/DBP at baseline, mm Hg	Intervention *vs.* control	Primary outcome	Major findings on blood pressure goals
Hemorrhagic stroke								
Anderson (INTERACT-1), 2008[60]	6 h	203/201	61/69	63/62	180/101 vs. 182/105	Intensive (<140 mm Hg) vs. standard (<180 mm Hg)	Proportional change in hematoma volume at 24 h	Intensive treatment was feasible and tolerated, and reduced hematoma growth.
Anderson (INTERACT-2), 2013[61]	6 h	1399/1430	64.2/61.7	63/64	179/101 vs. 179/101	Intensive (<140 mm Hg within 1 h) vs. standard (<180 mm Hg)	Death or major disability (mRS 3–6) at 90 days	Intensive treatment did not result in a significant reduction in death and severe disability.
Qureshi (ATACH-2), 2016[62]	4.5 h	500/500	60.8/63.2	62.0/61.9	200/- vs. 201/-	Intensive (SBP 110–139 mm Hg) vs. standard (SBP 140–179 mm Hg)	Mortality or dependency (mRS 4–6) at 3 months	Intensive treatment did not result in a lower rate of outcome than standard treatment.
Gupta, 2018[63]	72 h	59/59	66/77	65.1/62.8	175.1/109.8 vs. 178.5/111.7	Tight MAP control (<115 mm Hg) vs. conventional control (<130 mm Hg)	mRS at 90 days	MAP can be lowered to ≤ 115 mm Hg without increasing the odds of a poor clinical outcome at 90 days.
Ischemic stroke								
He (CATIS), 2014[64]	48 h	2038/2033	64.6/63.3	62.1/61.8	166.7/96.8 vs. 165.6/96.5	Lowering SBP 10–25% within the first 24 h and SBP/DBP < 140/90 mm Hg within 7 days vs. discontinue antihypertensive drugs	Mortality or dependency (mRS > 3) at 2 weeks or discharge	Primary outcome did not differ between treatment groups (mean SBP at day 7 was 137.3 and 146.5 mm Hg in the active and control groups, respectively).
Anderson (ENCHANTED), 2019[65]	6 h	1081/1115	62.9/61.1	66.7/67.1	165.4/91.2 vs. 165.2/90.7	Intensive (SBP 130–140 mm Hg within 1 h) vs. standard (SBP < 180 mm Hg)	Functional status (mRS) at 3 months	Intensive treatment did not result in a lower rate of outcome than standard treatment.
Nasi (MAPAS), 2019[66]	12 h	77/75/66	56/57/47	68/69/67	153/- vs. 163/- vs. 178/-	Maintain SBP during 24 h within: 140–160 mm Hg vs. 161–180 mm Hg vs. 181–200 mm Hg.	Favorable outcome (mRS 0–2) at 3 months	Targeting SBP 160–180 mm Hg tended to have favorable outcome; ICH occurred more frequently in Group 3 (181–200 mm Hg).
Mazighi (BP-TARGET), 2021[67]	Post MT	158/160	51/45	77/76	155/86 vs. 152/85	Intensive (SBP 100–129 mm Hg) vs. standard (SBP 130–185 mm Hg	The rate of radiographic intraparenchymal hemorrhage at 24–36 h	Intensive SBP target after successful endovascular therapy did not reduce the rate of radiographic intraparenchymal hemorrhage at 24–36 h as compared with the standard SBP target.

Table 3. Continued

First author and year of publication	Time window[a]	No. of patients	Men (%)	Mean age at baseline, years	Mean SBP/DBP at baseline, mm Hg	Intervention *vs.* control	Primary outcome	Major findings on blood pressure goals
Mixed hemorrhagic and ischemic stroke								
Potter (CHHIPS), 2009[68]	36 h	113/59	57/53	74/74	182/95 vs. 181/96	Active treatment (labetalol or lisinopril, targeting SBP 145–155 mm Hg or a reduction 15 mm Hg) vs. placebo	Mortality or dependency (mRS > 3) at 2 weeks	Active treatment did not influence the primary outcome, but reduced mortality at 3 months.
Robinson (COSSACS), 2010[69]	48 h	379/384	55/56	74/74	149/80 vs. 150/81	Continue vs. stop pre-existing antihypertensive drug treatment	Mortality or dependency (mRS > 3) at 2 weeks	Continued treatment lowered SBP/DBP (140/76 mm Hg) and did not increase adverse events, compared to stopped treatment (153/84 mm Hg)
Sandset (SCAST), 2011[70]	30 h	1017/1012	60/56	71/71	171.2/90.3 vs. 171.6/90.6	Candesartan vs. placebo	Composite endpoint (vascular death, MI, or stroke) and mRS at 6-months	Active treatment (147/82 mm Hg) had a higher risk of poor functional outcome than control group (152/84 mm Hg), but similar risk for composite vascular endpoint.
Yuan (CHASE), 2021[71]	72 h	242/241	55.8/55.6	66.4/66.0	174.3/96.6 vs. 173.1/97.2	Individualized treatment (with 10–15% ↓ in SBP 130–180 mm Hg within 2 h and maintain for 1 week) vs. standard (SBP < 200 mm Hg in AIS and < 180 mm Hg in ICH within 1 week)	Dependency (mRS > 3) at 3 months	Individualized treatment did not result in a lower rate of outcome than standard treatment.

Studies are listed in the order of the year of publication with each subsection. For explanations on the acronyms of trials, see the text.

Abbreviations: AIS, acute ischemic stroke; DBP, diastolic blood pressure; ICH, intracerebral hemorrhage; MI, myocardial infarction; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

[a]Time windows refers to time from the onset of stroke to admission.

Hemorrhagic Stroke

Four randomized controlled trials investigated blood pressure targets in acute hemorrhagic stroke.[60–63] In 3 trials, patients with an acute intracerebral hemorrhage within 4.5 to 6 hours were enrolled, and the goal of intensive blood pressure lowering was a systolic blood pressure below 140 mm Hg.[60–62] In another trial, patients with less acute hemorrhagic stroke within 72 hours were enrolled, and the goal of intensive blood pressure lowering was a mean arterial pressure below 115 mm Hg.[63]

The INTERACT-1 trial tested the feasibility of early lowering of elevated blood pressure in 404 patients with an acute intracerebral hemorrhage within 6 hours of onset and elevated systolic blood pressure (150–220 mm Hg).[60] Intensive blood pressure lowering treatment (target systolic blood pressure 140 mm Hg) reduced systolic blood pressure to 153 mm Hg at 1 hour from randomization and 146 mm Hg from 1 to 24 hours after randomization. The corresponding differences were 13.3 mm Hg and 10.8 mm Hg, respectively, from that of the standard guideline-based blood pressure management group (target systolic blood pressure 180 mm Hg). Proportional change in hematoma volume at 24 hours after randomization, which was the primary endpoint, tended to be smaller in the intensive than standard blood pressure lowering group (13.7% *vs.* 36.3%, $P = 0{\cdot}04$).

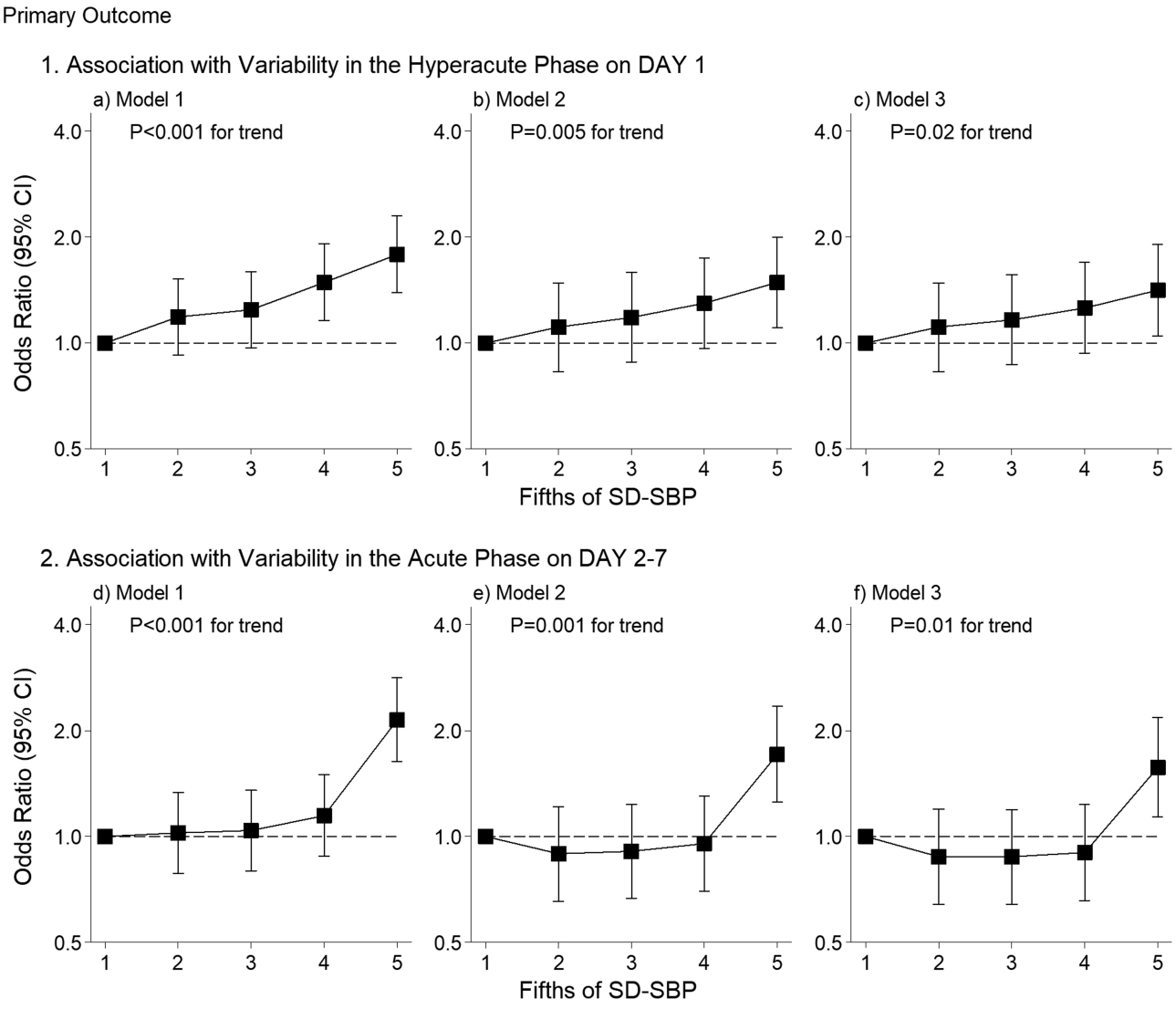


Figure 2. Association of hyperacute (D1, upper part) and acute (D2–7, lower part) standard deviation of systolic blood pressure (SBP) by fifths and primary outcome of death or dependency at 90 days. Standard deviation (SD) was estimated using 5 measurements at 1, 6, 12, 18, and 24 hours in the hyperacute phase on Day 1, and 12 measurements from Day 2 to 7 (morning and evening each day) in the acute phase on Day 2–7, respectively. Model 1 was adjusted for age, sex, and randomized group (left panels). Model 2 was adjusted for variables in model 1 plus region, hematoma volume at baseline, high scores on the National Institutes of Health Stroke Scale (middle panels). Model 3 was adjusted for all variables in model 2 and mean SBP in each phase (right panels). The range of SD for each group was < 8.1, 8.1 to 11.4, 11.5 to 15.0, 15.1 to 19.9, ≥20.0, respectively, for hyperacute phase, <8.8, 8.8 to 11.3, 11.4 to 13.7, 13.8 to 17.0, ≥17.1, respectively, for acute phase. Reproduced with permission from reference 72.

Intensive blood pressure lowering treatment did not alter the risks of adverse events or secondary clinical outcomes at 90 days. The trial showed that early intensive blood pressure lowering treatment was clinically feasible and well tolerated,[60] and built the basis for an outcome trial.

The INTERACT-2 trial had a similar design as the INTERACT-1 trial,[60] but was an outcome study.[61] The primary endpoint was death or major disability (a score of 3 to 6 on the modified Rankin scale, in which a score of 0 indicates no symptoms, a score of 5 indicates severe disability, and a score of 6 indicates death) at 90 days. In 2,794 patients with a spontaneous intracerebral hemorrhage within 6 hours of onset and elevated systolic blood pressure (150–220 mm Hg), intensive blood pressure lowering (targeting systolic blood pressure 140 mm Hg) did not result in a significant reduction in the rate of mortality and disability (odds ratio 0.87, $P = 0.06$). An ordinal analysis, however, showed significantly lower modified Rankin scores with intensive treatment (odds ratio for greater disability 0.87, $P = 0.04$), indicating improved functional outcomes with intensive blood pressure lowering.[61] The results of several post-hoc analyses of INTERACT-2 suggested that lower blood pressure variability (Figure 2)[72] and lower achieved blood pressure level (Figure 3)[73] were associated with favorable clinical outcomes and raised hypotheses for future research.

The ATACH-2 trial was in design similar to the INTERACT-2 trial,[61] but administered a standardized blood pressure lowering regimen with intravenous nicardipine to lower blood pressure to a systolic blood-pressure target of 110 to 139 mm Hg (intensive treatment) or a target of 140 to 179 mm Hg (standard treatment) in patients with an acute intracerebral hemorrhage within 4.5 hours after symptom onset.[62] Enrollment was stopped because of futility after a prespecified interim analysis in 1,000 randomized patients. The mean minimum systolic blood pressure during the first 2 hours was 128.9 mm Hg and 141.1 mm Hg in the intensive and standard-treatment groups, respectively. The primary outcome (death or disability, defined by modified Rankin scale score of 4 to 6, at 3 months after randomization) was not different between the 2 treatment groups (intensive vs. standard, relative risk 1.04, 95% confidence interval 0.85–1.27). However, the rate of renal adverse events within 7 days after randomization was significantly higher in the intensive-treatment than standard-treatment group (9.0% vs. 4.0%, $P = 0.002$).

Around similar period of time, a multicentric trial was conducted in India in 118 randomized patients with spontaneous intracerebral hemorrhage within 72 hours of onset to compare tight (target mean arterial pressure 115 mm Hg) with conventional blood pressure control (target mean arterial pressure 130 mm Hg).[63] Mean arterial pressure was 110 mm Hg and 120 mm Hg in the intensive and conventional blood pressure control groups, respectively. The primary outcome was not different between the 2 blood pressure control groups (median modified Rankin Scale at 90 days, 3 in both groups).[63]

Ischemic Stroke

Trials in patients with an acute ischemic stroke are divergent in the recruitment of study participants, such as the time window after stroke or the use of arterial mechanical thrombectomy.[64–67] The Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) enrolled patients with a very acute ischemic stroke within 6 hours,[65] and the other 3 trials enrolled patients with an acute ischemic stroke within 12[66] or 48 hours[64] or after successful reperfusion by arterial mechanical thrombectomy.[67]

The China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) enrolled 4,071 patients with an acute ischemic stroke within 48 hours of onset and elevated systolic blood pressure (140–219 mm Hg) to investigate whether blood pressure reduction (targeting systolic blood pressure for a reduction by 10% to 25% within the first 24 hours after randomization and to 140/90 mm Hg within 7 days) would prevent death and disability (modified Rankin Scale ≥ 3) at 14 days or at discharge.[64] Mean time from stroke onset to randomization was 15 hours. Mean systolic blood pressure was reduced from 166.7 mm Hg at randomization to

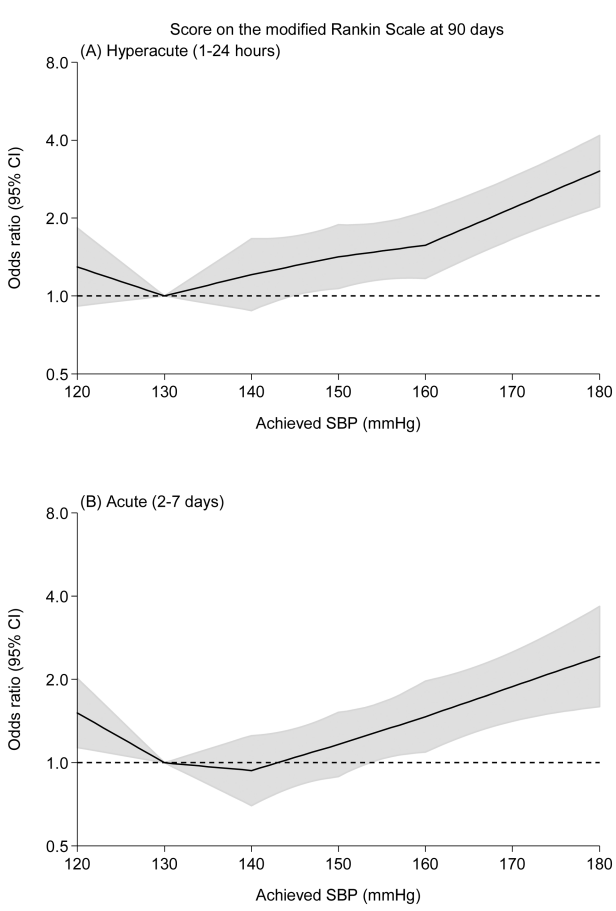


Figure 3. Effects of achieved systolic blood pressure (SBP, A: 1–24 hours, B: 2–7 days) on score of the modified Rankin Scale at 90 days. Odds ratios and 95% confidence intervals (CI, shaded areas) were estimated using ordinal analyses and were shown according to achieved SBP after adjustment for age, sex, region, time from onset to randomization, the National Institutes of Health Stroke Scale score, volume and location of hematoma, intraventricular extension, and randomized treatment. The reference was achieved systolic blood pressure of 130 mm Hg. Reproduced with permission from reference 73.

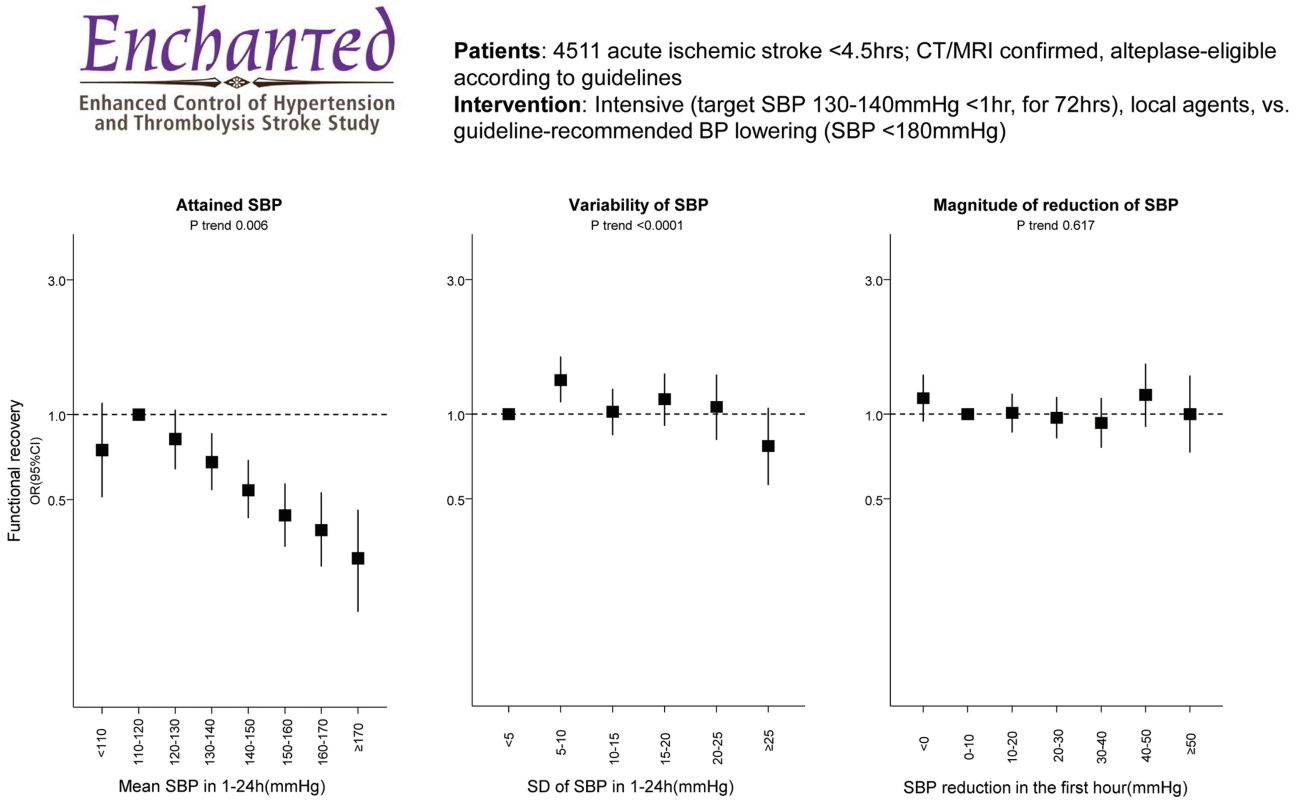


Figure 4. Associations of categorical systolic blood pressure (SBP) summary measures and outcomes. Odds ratio (OR) and 95% confidence interval (CI) are comparisons between each category and the reference, adjusted for age (<65 vs. ≥65), sex, ethnicity (Asian vs. non-Asian), degree of neurological impairment (the National Institutes of Health Stroke Scale score < 8 vs. ≥8), pre-morbid function (modified Rankin scale scores 0 vs. 1), pre-morbid use of antithrombotic agents (aspirin, other antiplatelet agent, or warfarin] and antihypertensive agents, and history of hypertension, stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomized treatment (intensive blood pressure control, guideline-recommended blood pressure control, low-dose alteplase, and standard-dose alteplase). Patients: 4511 acute ischemic stroke <4.5 hrs; CT/MRI confirmed, alteplase-eligible according to guidelines. Intervention: intensive (target SBP 130–140 mm Hg <1 hr, for 72 hrs), local agents, vs. guideline-recommended BP lowering (SBP < 180 mm Hg). Attaining early and consistent reductions in SBP to levels <140 mm Hg, even as low as 110–120 mm Hg, over 24 hours is associated with better outcomes in thrombolyzed patients with acute ischemic stroke at 90 days. *Any intracranial hemorrhage (ICH) within 7 days. †Death or neurologic deterioration defined as an increase of ≥ 4 points on the National Institutes of Health Stroke Scale or a decline of ≥ 2 on the Glasgow Coma Scale within 7 days post-randomization. ‡Any serious adverse event (SAE) within 90 days. Reproduced with permission from reference 74.

144.7 mm Hg (−12.7%) within 24 hours and to 137.3 mm Hg at 7 days after randomization in the antihypertensive treatment group. The corresponding values in the non-antihypertensive treatment control group were 165.6 mm Hg, 152.9 mm Hg (−7.2%) and 146.5 mm Hg, respectively. The between-group differences were 9.1 mm Hg within 24 hours and 9.3 mm Hg at 7 days. The 2 groups did not differ for death and major disability at 14 days or hospital discharge (primary outcome, odds ratio 1.00, $P = 0.98$)) nor at 3-month post-treatment follow-up (secondary outcome, odds ratio 0.99, $P = 0.93$).[64]

The ENCHANTED trial enrolled 2,196 thrombolysis-eligible patients with acute ischemic stroke within 6 hours of stroke onset and elevated systolic blood pressure (≥150 mm Hg) to compare intensive (target systolic blood pressure 130–140 mm Hg within 1 hour) with guideline-based (target systolic blood pressure < 180 mm Hg) blood pressure lowering treatment over 72 hours.[65] 2,175 of the 2,196 randomized patients actually received intravenous alteplase. Median time from stroke onset to randomization was 3.3 hours. Mean systolic blood pressure over 24 hours was 144.3 mm Hg and 149.8 mm Hg in the intensive and guideline groups, respectively. The primary outcome (functional status at 90 days measured by shift in modified Rankin scale scores) did not differ between the 2 groups (intensive versus guideline-based treatment, odds ratio 1.01, $P = 0.87$). However, fewer patients in the intensive group than in the guideline group had an intracranial hemorrhage (odds ratio 0.75, $P = 0{\cdot}01$).[65] The results of a post hoc analysis of ENCHANTED showed that lower blood pressure variability and lower achieved blood pressure level might be associated with a favorable outcome (Figure 4).[74]

The early Manipulation of Arterial blood Pressure in Acute ischemic Stroke (MAPAS) trial enrolled 218 patients with an acute ischemic stroke within 12 hours of onset to

compare three systolic blood pressure ranges during 24 hours (140–160 mm Hg, 161–180 mm Hg, and 181–200 mm Hg).[66] With the possible use of vasoactive drugs and fluids to achieve the targets, the median systolic blood pressure in the 3 groups in 24 hours was 153 mm Hg, 163 mm Hg, and 178 mm Hg, respectively. Good outcome, defined as a modified Rankin Scale score 0-2 at 90 days, did not differ between the 3 groups ($P = 0.27$). Symptomatic intracranial hemorrhage was significantly more frequent in the higher than medium and lower systolic blood pressure range groups ($P = 0.048$).[66]

The BP-TARGET trial enrolled 423 patients with an acute ischemic stroke that was attributable to a large-vessel occlusion and had successfully reperfusion with endovascular therapy to assess whether an intensive systolic blood pressure target (100–129 mm Hg) would result in a lower rate of intraparenchymal hemorrhage than a standard systolic blood pressure target (130–185 mm Hg).[67] The target systolic blood pressure had to be achieved within 1 hour after randomization and maintained for 24 hours with intravenous blood pressure lowering agents. The mean systolic blood pressure during the first 24 hours after reperfusion was 128 mm Hg and 138 mm Hg in the intensive and standard target groups, respectively. The 2 groups were not significantly different for the primary outcome (the rate of radiographic intraparenchymal hemorrhage at 24–36 hours, intensive versus standard treatment, odds ratio 0.96, $P = 0{\cdot}84$) nor the primary safety outcome (the occurrence of hypotension) or mortality within the first week after randomization.[67]

Mixed Hemorrhagic and Ischemic Stroke

Four trials included both patients with an acute hemorrhagic stroke and those with an acute ischemic stroke in acute or subacute phase (within 30 to 72 hours of onset).[68–71] Of these 4 trials, 2 compared certain antihypertensive drugs with placebo,[68,70] 1 compared continuation and discontinuation of antihypertensive drug treatment,[69] and 1 compared intensive with standard blood pressure lowering target.[71]

The controlling hypertension and hypotension immediately post-stroke (CHHIPS) trial was a placebo-controlled double-blind pilot study.[68] It enrolled 179 patients with cerebral infarction or cerebral hemorrhage within 36 hours of onset and elevated systolic blood pressure (>160 mm Hg) to receive oral or intravenous labetalol, oral or sublingual lisinopril, or placebo. The doses were titrated up to achieve the target systolic blood pressure (145–155 mm Hg or a reduction of 15 mm Hg from baseline). There was a significantly greater fall in systolic blood pressure within the first 24 hours in the active treatment groups than the placebo group (21 vs. 11 mm Hg). The primary outcome (death or dependency at 2 weeks) was not different between the 2 groups (treatment vs. placebo, relative risk 1.03, $P = 0.82$). Active treatment did not increase the risk of early neurological deterioration ($P = 0.76$), but tended to reduce 3-month mortality compared with placebo (hazard ratio 0·40, $P = 0.05$).[68]

The Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS) enrolled 763 patients who were taking antihypertensive drugs and had a stroke within 48 hours of onset to compare continuation with discontinuation of pre-existing antihypertensive drugs for 2 weeks.[69] Systolic/diastolic blood pressure at 2 weeks was on average 13/8 mm Hg lower in the continuation than discontinuation group. The continuation and discontinuation groups were not different for the primary endpoint (death or dependency at 2 weeks, a modified Rankin scale score > 3 points, continuation vs. discontinuation, relative risk 0.86, $P = 0.3$) nor serious adverse events, 6-month mortality, or major cardiovascular events.[69]

The Scandinavian Candesartan Acute Stroke Trial (SCAST) enrolled 2,029 patients with an acute stroke within 30 hours of onset and elevated systolic blood pressure (≥140 mm Hg) to be treated with either candesartan or placebo for 7 days, with doses increasing from 4 mg on day 1 to 16 mg on days 3 to 7.[70] The mean systolic/diastolic blood pressures at 7 days of treatment were 147/82 mm Hg and 152/84 mm Hg in the candesartan and placebo groups, respectively. During 6 months follow-up, the 2 groups had similar risks of the composite vascular endpoint (candesartan vs. placebo, hazard ratio 1.09, $P = 0.52$), but the candesartan group had a higher risk of poor outcome than the placebo group (odds ratio 1.17, $P = 0.048$).[70]

The Controlling Hypertension After Severe Cerebrovascular Event (CHASE) trial enrolled 483 patients with an acute severe (a Glasgow Coma Scale score ≤ 12 or a National Institutes of Health Stroke Scale score ≥ 11) stroke within 72 hours of onset and elevated systolic blood pressure (150–210 mm Hg) to compare a so-called individualized (10–15% reduction in systolic blood pressure from admission achieved within 2 hours and maintained for a week) with a standard systolic blood pressure lowering group (target < 200 mm Hg in acute ischemic stroke and < 180 mm Hg in intracerebral hemorrhage).[71] Mean values of systolic blood pressure in the individualized and standard treatment groups were 151.6 mm Hg (12.9% reduction from baseline) and 160.7 mm Hg (6.3% reduction from baseline), respectively, at 2 hours, 144.0 mm Hg (17.0% reduction from baseline) and 148.2 mm Hg (13.3% reduction from baseline), respectively, at 24 hours, and 138.1 mm Hg (20.5% reduction from baseline) and 139.7 mm Hg (18.1% reduction from baseline), respectively, at 7 days. The primary outcome (the proportion of patients with a poor functional outcome at day 90 of enrolment) was non-significantly lower in the individualized than standard treatment group (odds ratio 0.75; $P = 0.22$).[71]

CONCLUSIONS AND PERSPECTIVES

Current guideline recommendations on the blood pressure goals in acute stroke are clinically empirical and generally rather conservative. Antihypertensive treatment is recommended only in severe hypertension. Observational studies showed that the relationship between blood pressure and unfavorable clinical outcomes was probably positive in acute hemorrhagic stroke but J- or U-shaped in acute ischemic stroke with undetermined nadir blood pressure. The results of randomized controlled trials are promising

for blood pressure management in hemorrhagic stroke but less so in ischemic stroke. A systolic blood pressure goal of 140 mm Hg is probably appropriate for acute hemorrhagic stroke. The blood pressure goal in acute ischemic stroke, however, remains uncertain, and probably depends on the time window of treatment and the use of revascularization therapy.

Further research is required to investigate the potential benefit of antihypertensive treatment in acute stroke. When such trials are designed, the time window is of paramount importance. In the very early phase of acute stroke, blood pressure variability might be even more important than blood pressure level. Future studies may address whether it is possible to treat increased blood pressure variability and whether such treatment confers any outcome benefit.[75] In the subacute phase of a stroke, blood pressure lowering might be more likely beneficial with a very intensive blood pressure goal, such as, for instance, 130/80 mm Hg.

DISCLOSURE

Wang reports having received lecture and consulting fees from Novartis, Omron, and Servier. The other authors declared no conflict of interest.

FUNDING

Qian-Hui Guo and Ji-Guang Wang was financially supported by grants from the National Natural Science Foundation of China (91639203, 82070435, and 82000394), and Ministry of Science and Technology (2018YFC1704902), Beijing, China and from the Shanghai Commission of Science and Technology (19DZ2340200) and Shanghai Commission of Health ("Three-year Action Program of Shanghai Municipality for Strengthening the Construction of Public Health System" GWV-10.1-XK05 and a special grant for "leading academics"), and the Clinical Research Program, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (grant 2018CR010), Shanghai, China.

REFERENCES

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2021; 20:795–820.
2. Ma Q, Li R, Wang L, Yin P, Wang Y, Yan C, Ren Y, Qian Z, Vaughn MG, McMillin SE, Hay SI, Naghavi M, Cai M, Wang C, Zhang Z, Zhou M, Lin H, Yang Y. Temporal trend and attributable risk factors of stroke burden in China, 1990-2019: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health* 2021; 6:e897–e906.
3. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990; 335:827–838.
4. Staessen JA, Gasowski J, Wang JG, Thijs L, Den HE, Boissel JP, Coope J, Ekbom T, Gueyffier F, Liu L, Kerlikowske K, Pocock S, Fagard RH. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000; 355:865–872.
5. Joint Committee for Guideline Revision. 2018 Chinese guidelines for prevention and treatment of hypertension-a report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. *J Geriatr Cardiol* 2019; 16:182–241.
6. Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, Horio T, Hoshide S, Ikeda S, Ishimitsu T, Ito M, Ito S, Iwashima Y, Kai H, Kamide K, Kanno Y, Kashihara N, Kawano Y, Kikuchi T, Kitamura K, Kitazono T, Kohara K, Kudo M, Kumagai H, Matsumura K, Matsuura H, Miura K, Mukoyama M, Nakamura S, Ohkubo T, Ohya Y, Okura T, Rakugi H, Saitoh S, Shibata H, Shimosawa T, Suzuki H, Takahashi S, Tamura K, Tomiyama H, Tsuchihashi T, Ueda S, Uehara Y, Urata H, Hirawa N. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2019). *Hypertens Res* 2019; 42:1235–1481.
7. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I; Authors/Task Force Members. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018; 36:1953–2041.
8. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, Wainford RD, Williams B, Schutte AE. 2020 International Society of Hypertension global hypertension practice guidelines. *Hypertension* 2020; 75:1334–1357.
9. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018; 71:1269–1324.
10. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360:1903–1913.
11. Li Y, Thijs L, Zhang ZY, Asayama K, Hansen TW, Boggia J, Björklund-Bodegård K, Yang WY, Niiranen TJ, Ntineri A, Wei FF, Kikuya M, Ohkubo T, Dolan E, Hozawa A, Tsuji I, Stolarz-Skrzypek K, Huang QF, Melgarejo JD, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Aparicio L, Barochiner J, Gilis-Malinowska N, Narkiewicz K, Kawecka-Jaszcz K, Maestre GE, Jula AM, Johansson JK, Kuznetsova T, Filipovský J, Stergiou G, Wang JG, Imai Y, O'Brien E, Staessen JA; International Database on Ambulatory and Home Blood Pressure in Relation to Cardiovascular Outcome Investigators. Opposing age-related trends in absolute and relative risk of adverse health outcomes associated with out-of-office blood pressure. *Hypertension* 2019; 74:1333–1342.
12. Kang YY, Wang JG. The J-curve phenomenon in hypertension. *Pulse (Basel)* 2016; 4:49–60.
13. Cruickshank JM. Coronary flow reserve and the J curve relation between diastolic blood pressure and myocardial infarction. *BMJ* 1988; 297:1227–1230.
14. Messerli FH, Panjrath GS. The J-curve between blood pressure and coronary artery disease or essential hypertension: exactly how essential? *J Am Coll Cardiol* 2009; 54:1827–1834.
15. Wang JG, Li Y. Primary and secondary prevention of stroke by antihypertensive drug treatment. *Expert Rev Neurother* 2004; 4:1023–1031.
16. PATS Collaborating Group. Post-stroke antihypertensive treatment study. A preliminary result. *Chin Med J (Engl)* 1995; 108:710–717.
17. Liu L, Wang Z, Gong L, Zhang Y, Thijs L, Staessen JA, Wang J. Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature. *Hypertens Res* 2009; 32:1032–1040.
18. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals

with previous stroke or transient ischaemic attack. *Lancet* 2001; 358:1033–1041.
19. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001; 358:1305–1315.
20. Yusuf S, Diener HC, Sacco RL, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlöf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, VanderMaelen C, Voigt T, Weber M, Yoon BW; PRoFESS Study Group. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008; 359:1225–1237.
21. SPS3 Study Group; Benavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, Pearce LA, Pergola PE, Szychowski JM. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013; 382:507–515.
22. Sandset EC, Anderson CS, Bath PM, Christensen H, Fischer U, Gąsecki D, Lal A, Manning LS, Sacco S, Steiner T, Tsivgoulis G. European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. *Eur Stroke J* 2021; 6:II.
23. Hemphill JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, MacDonald RL, Mitchell PH, Scott PA, Selim MH, Woo D. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2015; 46:2032–2060.
24. Shoamanesh A, Patrice Lindsay M, Castellucci LA, Cayley A, Crowther M, de Wit K, English SW, Hoosein S, Huynh T, Kelly M, O'Kelly CJ, Teitelbaum J, Yip S, Dowlatshahi D, Smith EE, Foley N, Pikula A, Mountain A, Gubitz G, Gioia LC. Canadian stroke best practice recommendations: Management of Spontaneous Intracerebral Hemorrhage, 7th Edition Update 2020. *Int J Stroke* 2021; 16:321–341.
25. Boulanger JM, Lindsay MP, Gubitz G, Smith EE, Stotts G, Foley N, Bhogal S, Boyle K, Braun L, Goddard T, Heran M, Kanya-Forster N, Lang E, Lavoie P, McClelland M, O'Kelly C, Pageau P, Pettersen J, Purvis H, Shamy M, Tampieri D, vanAdel B, Verbeek R, Blacquiere D, Casaubon L, Ferguson D, Hegedus Y, Jacquin GJ, Kelly M, Kamal N, Linkewich B, Lum C, Mann B, Milot G, Newcommon N, Poirier P, Simpkin W, Snieder E, Trivedi A, Whelan R, Eustace M, Smitko E, Butcher K. Canadian stroke best practice recommendations for acute stroke management: prehospital, emergency department, and acute inpatient stroke care, 6th Edition, Update 2018. *Int J Stroke* 2018; 13:949–984.
26. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019 Update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019; 50:e344–e418.
27. Koga M, Toyoda K, Yamagami H, Okuda S, Okada Y, Kimura K, Shiokawa Y, Nakagawara J, Furui E, Hasegawa Y, Kario K, Osaki M, Miyagi T, Endo K, Nagatsuka K, Minematsu K. Systolic blood pressure lowering to 160 mmHg or less using nicardipine in acute intracerebral hemorrhage: a prospective, multicenter, observational study (the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement-Intracerebral Hemorrhage study). *J Hypertens* 2012; 30:2357–2364.
28. Sakamoto Y, Koga M, Yamagami H, Okuda S, Okada Y, Kimura K, Shiokawa Y, Nakagawara J, Furui E, Hasegawa Y, Kario K, Arihiro S, Sato S, Kobayashi J, Tanaka E, Nagatsuka K, Minematsu K, Toyoda K. Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: the stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. *Stroke* 2013; 44:1846–1851.
29. Rodriguez-Luna D, Muchada M, Piñeiro S, Flores A, Rubiera M, Pagola J, Coscojuela P, Meler P, Sanjuan E, Boned-Riera S, Cárcamo DA, Tomasello A, Alvarez-Sabin J, Ribo M, Molina CA. Potential blood pressure thresholds and outcome in acute intracerebral hemorrhage. *Eur Neurol* 2014; 72:203–208.
30. Mustanoja S, Putaala J, Koivunen RJ, Surakka I, Tatlisumak T. Blood pressure levels in the acute phase after intracerebral hemorrhage are associated with mortality in young adults. *Euro J Neurol* 2018; 25:1034–1040.
31. Zhao JL, Du ZY, Sun YR, Yuan Q, Yu J, Wu X, Li ZQ, Wu XH, Xie R, Hu J. Intensive blood pressure control reduces the risk of progressive hemorrhage in patients with acute hypertensive intracerebral hemorrhage: a retrospective observational study. *Clin Neurol Neurosurg* 2019; 180:1–6.
32. Francoeur CL, Mayer SA. Acute blood pressure and outcome after intracerebral hemorrhage: The VISTA-ICH Cohort. *J Stroke Cerebrovasc Dis* 2021; 30:105456.
33. Castillo J, Leira R, García MM, Serena J, Blanco M, Dávalos A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. *Stroke* 2004; 35:520–526.
34. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Manios E, Konstantopoulou P, Mavrikakis M. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Internl Med* 2004; 255:257–265.
35. Abboud H, Labreuche J, Plouin F, Amarenco P. High blood pressure in early acute stroke: a sign of a poor outcome? *J Hypertens* 2006; 24:381–386.
36. Sartori M, Benetton V, Carraro AM, Calò LA, Macchini L, Giantin V, Tosato F, Pessina AC, Semplicini A. Blood pressure in acute ischemic stroke and mortality: a study with noninvasive blood pressure monitoring. *Blood Press Monit* 2006; 11:199–205.
37. Armario P, Martín-Baranera M, Ceresuela LM, Del Rey RH, Iribarnegaray E, Pintado S, Avila A, Bello J, Tovar JL, Alvarez-Sabin J. Blood pressure in the initial phase of acute ischaemic stroke: evolution and its role as an independent prognosis factor at discharge and after 3 months of follow-up. *Blood Press* 2008; 17:284–290.
38. Weiss A. Systolic blood pressure during the first day of stroke predicts short-term functional status and long term mortality in elderly patients. *Eur J Intern Med* 2013; 24:e47.
39. Hao Z, Liu M, Wang D, Wu B, Tao W, Chang X. High blood pressure on admission in relation to poor outcome in acute ischemic stroke with intracranial atherosclerotic stenosis or occlusion. *J Stroke Cerebrovasc Dis* 2014; 23:1403–1408.
40. Ishitsuka K, Kamouchi M, Hata J, Fukuda K, Matsuo R, Kuroda J, Ago T, Kuwashiro T, Sugimori H, Nakane H, Kitazono T. High blood pressure after acute ischemic stroke is associated with poor clinical outcomes: Fukuoka Stroke Registry. *Hypertension* 2014; 63:54–60.
41. Wohlfahrt P, Krajcoviechova A, Jozifova M, Mayer O, Vanek J, Filipovsky J, Cifkova R. Low blood pressure during the acute period of ischemic stroke is associated with decreased survival. *J Hypertens* 2015; 33:339–345.
42. Mustanoja S, Putaala J, Gordin D, Tulkki L, Aarnio K, Pirinen J, Surakka I, Sinisalo J, Lehto M, Tatlisumak T. Acute-phase blood pressure levels correlate with a high risk of recurrent strokes in young-onset ischemic stroke. *Stroke* 2016; 47:1593–1598.
43. Bangalore S, Schwamm L, Smith EE, Hellkamp AS, Suter RE, Xian Y, Schulte PJ, Fonarow GC, Bhatt DL. Blood pressure and in-hospital outcomes in patients presenting with ischaemic stroke. *Eur Heart J* 2017; 38:2827–2835.
44. Kang J, Kim BJ, Han MK, Bae HJ. The changing effect of blood pressure on stroke outcomes through acute to subacute stage of ischemic stroke. *J Stroke Cerebrovasc Dis* 2019; 28:2563–2568.
45. Ajinkya S, Almallouhi E, Turner N, Al Kasab S, Holmstedt CA. The relationship between admission systolic blood pressure and mortality in telestroke patients. *Telemed J E Health* 2020; 26:941–944.
46. Wu L, Huang X, Wu D, Zhao W, Wu C, Che R, Zhang Z, Jiang F, Bian T, Yang T, Dong K, Zhang Q, Yu Z, Ma Q, Song H, Ding Y, Ji X. Relationship between post-thrombolysis blood pressure and outcome in acute ischemic stroke patients undergoing thrombolysis therapy. *J Stroke Cerebrovasc Dis* 2017; 26:2279–2286.
47. He M, Wang H, Tang Y, Cui B, Xu B, Sun Y, Zhang G, He X, Niu X, Wang B, Xu B, Li Z, Hui R, Wang Y. Optimal blood pressure levels in different phases of peripheral thrombolysis period in acute ischemic stroke. *J Hypertens* 2021; 39:1453–1461.
48. Goyal N, Tsivgoulis G, Pandhi A, Chang JJ, Dillard K, Ishfaq MF, Nearing K, Choudhri AF, Hoit D, Alexandrov AW, Arthur AS, Elijovich L, Alexandrov AV. Blood pressure levels post mechanical

thrombectomy and outcomes in large vessel occlusion strokes. *Neurology* 2017; 89:540–547.
49. Maïer B, Gory B, Taylor G, Labreuche J, Blanc R, Obadia M, Abrivard M, Smajda S, Desilles JP, Redjem H, Ciccio G, Lukaszewicz AC, Turjman F, Riva R, Labeyrie PE, Duhamel A, Blacher J, Piotin M, Lapergue B, Mazighi M. Mortality and disability according to baseline blood pressure in acute ischemic stroke patients treated by thrombectomy: A Collaborative Pooled Analysis. *J Am Heart Assoc* 2017; 6:e006484.
50. Anadani M, Orabi Y, Alawieh A, Chatterjee A, Lena J, Al Kasab S, Spiotta AM. Blood pressure and outcome post mechanical thrombectomy. *J Clin Neurosci* 2019; 62:94–99.
51. Anadani M, Orabi MY, Alawieh A, Goyal N, Alexandrov AV, Petersen N, Kodali S, Maier IL, Psychogios MN, Swisher CB, Inamullah O, Kansagra AP, Giles JA, Wolfe SQ, Singh J, Gory B, De Marini P, Kan P, Nascimento FA, Freire LI, Pandhi A, Mitchell H, Kim JT, Fargen KM, Al Kasab S, Liman J, Rahman S, Allen M, Richard S, Spiotta AM. Blood pressure and outcome after mechanical thrombectomy with successful revascularization. *Stroke* 2019; 50:2448–2454.
52. van den Berg SA, Uniken Venema SM, Mulder M, Treurniet KM, Samuels N, Lingsma HF, Goldhoorn RB, Jansen IGH, Coutinho JM, Roozenbeek B, Dippel DWJ, Roos Y, van der Worp HB, Nederkoorn PJ. Admission blood pressure in relation to clinical outcomes and successful reperfusion after endovascular stroke treatment. *Stroke* 2020; 51:3205–3214.
53. An J, Tang Y, Cao X, Yuan H, Wei M, Yuan X, Zhang A, Li Y, Saguner A, Li G, Luo G. Systemic arterial blood pressure and intracerebral hemorrhage after mechanical thrombectomy in anterior cerebral circulation. *J Investig Med* 2021; 69:1008–1014.
54. Chen M, Kronsteiner D, Pfaff J, Schieber S, Jäger L, Bendszus M, Kieser M, Möhlenbruch MA, Ringleb PA, Bösel J, Schönenberger S. Hemodynamic status during endovascular stroke treatment: association of blood pressure with functional outcome. *Neurocrit Care* 2021; 35:825–834.
55. Gigliotti MJ, Padmanaban V, Richardson A, Simon SD, Church EW, Cockroft KM. Effect of blood pressure management strategies on outcomes in patients with acute ischemic stroke after successful mechanical thrombectomy. *World Neurosurg* 2021; 148:e635–e642.
56. Choi KH, Kim JM, Kim JH, Kim JT, Park MS, Choi SM, Lee SH, Kim BC, Kim MK, Cho KH. Optimal blood pressure after reperfusion therapy in patients with acute ischemic stroke. *Sci Rep* 2019; 9:5681.
57. Okumura K, Ohya Y, Maehara A, Wakugami K, Iseki K, Takishita S. Effects of blood pressure levels on case fatality after acute stroke. *J Hypertens* 2005; 23:1217–1223.
58. Zhang Y, Reilly KH, Tong W, Xu T, Chen J, Bazzano LA, Qiao D, Ju Z, Chen CS, He J. Blood pressure and clinical outcome among patients with acute stroke in Inner Mongolia, China. *J Hypertens* 2008; 26:1446–1452.
59. Furlan NE, Bazan SGZ, Braga GP, Castro M, Franco R, Gut AL, Bazan R, Martin LC. Association between blood pressure and acute phase stroke case fatality rate: a prospective cohort study. *Arq Neuropsiquiatr* 2018; 76:436–443.
60. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, Heeley E, Skulina C, Parsons MW, Kim JS, Tao QL, Li YC, Jiang JD, Tai LW, Zhang JL, Xu E, Cheng Y, Heritier S, Morgenstern LB, Chalmers J. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol* 2008; 7:391–399.
61. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, Hata J, Arima H, Parsons M, Li Y, Wang J, Heritier S, Li Q, Woodward M, Simes RJ, Davis SM, Chalmers J. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013; 368:2355–2365.
62. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, Toyoda K, Wang Y, Yamamoto H, Yoon BW. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med* 2016; 375:1033–1043.
63. Gupta S, Abbot AK, Srinath R, Tewari AK, Gupta A, Gorthi SP, Narayanan CS, Totlani SI, Sirohi YS, Anadure R. Randomized trial to assess safety and clinical efficacy of intensive blood pressure reduction in acute spontaneous intracerebral haemorrhage. *Med J Armed Forces India* 2018; 74:120–125.
64. He J, Zhang Y, Xu T, Zhao Q, Wang D, Chen CS, Tong W, Liu C, Xu T, Ju Z, Peng Y, Peng H, Li Q, Geng D, Zhang J, Li D, Zhang F, Guo L, Sun Y, Wang X, Cui Y, Li Y, Ma D, Yang G, Gao Y, Yuan X, Bazzano LA, Chen J. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. *JAMA* 2014; 311:479–489.
65. Anderson CS, Huang Y, Lindley RI, Chen X, Arima H, Chen G, Li Q, Billot L, Delcourt C, Bath PM, Broderick JP, Demchuk AM, Donnan GA, Durham AC, Lavados PM, Lee TH, Levi C, Martins SO, Olavarria VV, Pandian JD, Parsons MW, Pontes-Neto OM, Ricci S, Sato S, Sharma VK, Silva F, Song L, Thang NH, Wardlaw JM, Wang JG, Wang X, Woodward M, Chalmers J, Robinson TG. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. *Lancet* 2019; 393:877–888.
66. Nasi LA, Martins SCO, Gus M, Weiss G, de Almeida AG, Brondani R, Rebello LC, DalPizzol A, Fuchs FD, Valença MJM, Wirth LF, Nunes G, Anderson CS. Early manipulation of arterial blood pressure in acute ischemic stroke (MAPAS): Results of a randomized controlled trial. *Neurocrit Care* 2019; 30:372–379.
67. Mazighi M, Richard S, Lapergue B, Sibon I, Gory B, Berge J, Consoli A, Labreuche J, Olivot JM, Broderick J, Duhamel A, Touze E, Qureshi AI, Yavchitz A, Escalard S, Desilles JP, Redjem H, Smajda S, Fahed R, Hébert S, Maïer B, Delvoye F, Boursin P, Maacha MB, Obadia M, Sabben C, Blanc R, Savatovsky J, Piotin M. Safety and efficacy of intensive blood pressure lowering after successful endovascular therapy in acute ischaemic stroke (BP-TARGET): a multicentre, open-label, randomised controlled trial. *Lancet Neurol* 2021; 20:265–274.
68. Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, Jagger C. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol* 2009; 8:48–56.
69. Robinson TG, Potter JF, Ford GA, Bulpitt CJ, Chernova J, Jagger C, James MA, Knight J, Markus HS, Mistri AK, Poulter NR. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. *Lancet Neurol* 2010; 9:767–775.
70. Sandset EC, Bath PM, Boysen G, Jatuzis D, Kõrv J, Lüders S, Murray GD, Richter PS, Roine RO, Terént A, Thijs V, Berge E. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet* 2011; 377:741–750.
71. Yuan F, Yang F, Zhao J, Fu F, Liu Y, Xue C, Wang K, Yuan X, Li D, Liu Q, Zhang W, Jia Y, He J, Zhou J, Wang X, Lv H, Huo K, Li Z, Zhang B, Wang C, Li L, Li H, Jiang W. Controlling hypertension after severe cerebrovascular event (CHASE): A randomized, multicenter, controlled study. *Int J Stroke* 2021; 16:456–465.
72. Manning L, Hirakawa Y, Arima H, Wang X, Chalmers J, Wang J, Lindley R, Heeley E, Delcourt C, Neal B, Lavados P, Davis SM, Tzourio C, Huang Y, Stapf C, Woodward M, Rothwell PM, Robinson TG, Anderson CS; INTERACT2 Investigators. Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. *Lancet Neurol* 2014; 13:364–373.
73. Arima H, Heeley E, Delcourt C, Hirakawa Y, Wang X, Woodward M, Robinson T, Stapf C, Parsons M, Lavados PM, Huang Y, Wang J, Chalmers J, Anderson CS; INTERACT2 Investigators. Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT2. *Neurology* 2015; 84:464–471.
74. Wang X, Minhas JS, Moullaali TJ, Luca Di Tanna G, Lindley RI, Chen X, Arima H, Chen G, Delcourt C, Bath PM, Broderick JP, Demchuk AM, Donnan GA, Durham AC, Lavados PM, Lee TH, Levi C, Martins SO, Olavarria VV, Pandian JD, Parsons MW, Pontes-Neto OM, Ricci S, Sato S, Sharma VK, Silva F, Thang NH, Wang JG, Woodward M, Chalmers J, Song L, Anderson CS, Robinson TG; ENCHANTED Investigators. Associations of early systolic blood pressure control and outcome after thrombolysis-eligible acute ischemic stroke: results from the ENCHANTED study. *Stroke* 2022; 53(3):779–787.
75. Lattanzi S, Brigo F, Silvestrini M. Blood pressure variability and stroke: a risk marker of outcome and target for intervention. *J Clin Hypertens (Greenwich)* 2021; 23:103–105.