Evidence assessment on blood pressure management in spontaneous intracerebral hemorrhage: a scoping review

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Background

Clinical practice guidelines (CPGs) recommend the intensive antihypertensive reduction [blood pressure (BP) goal: <140 mmHg] for the management of blood pressure in spontaneous intracerebral hemorrhage (ICH) patients. However, clinical trials (CTs) and systematic reviews (SR) published after the most recent CPGs have issued different conclusions to the recommendations, maintaining the clinical debate on the decision of the best BP goal of treatment.

Methods

We systematically searched CPGs which have recommendations on BP management in patients with ICH. Additionally, we searched SRs and CTs that assessed the safeness and effectiveness of the intensive compared to the standard reduction (BP goal: 140-180 mmHg). The search was done in January 2019 in three databases (Medline/Pubmed, Scopus and CENTRAL), and there were no restrictions on language. Two independent authors selected the studies, extracted the information, and assessed the quality (AGREE-II for CPGs, AMSTAR-II for SRs, and RoB-2 for CTs).

Conclusions

Most of the assessed CPGs did not take into account the patient's viewpoints, but did have a high score in the rigor of development domain. CPGs support the use of the intensive reduction, however, recent SRs partially supported or did not support it. This can be due to the association with renal failure, and the risk of bias of the primary studies (CTs). We propose that using the intensive reduction can have the same effect as standard reduction, and may produce adverse effects in ICH patients, therefore standard reduction is the safest and most effective treatment to reduce high BP in ICH.

Results

We included three CPGs, of which 2/3 had a score ≥ 60% in the domain #3 (rigor of development), and 1/3 had a score ≥ 70% in the overall evaluation of AGREE-II; 1/3 used the GRADE methodology. We included seven SRs, of which 3/7 had a score ≥ 11 in AMSTAR-II. In addition, 2/7 totally supported the intensive reduction; 4/7 partially supported the intensive reduction (it fails to improve clinical outcomes, its evidence is insufficient, but appears to be safe), and 1/7 did not recommend it (lack of evidence). One SR found that intensive reduction is associated with renal failure (RR=2.18; 95%CI: 1.08-4.41). We included nine CTs, of which 1/9 was not randomized; 5/9 were open-label; and 4/9 had a high risk of bias arising from the randomization process in six outcomes. One CT used lisinopril and labetalol; other CT used nicardipine; and 7/9 CTs used any available BP lowering agent. The population was small (< 100 patients) in 3/9 CTs, and 2/9 studied ≥ 1000 patients.

Table 1. Recommendations of included clinical practice guidelines.

Included clinical practice guideline	Recommendation	Level of evidence	Grade of Recommendation	System of recommendation	Year of publication	Design of cited studies for recommendation	Year of search
AHA/ASA	For ICH patients presenting with SBP between 150 and 220 mmHg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe and can be effective for improving functional outcome.	I	A	ACC/AHA	2015	Clinical trials	2013
	For ICH patients presenting with SBP >220 mmHg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring.	IIb	C				
ESO	In acute ICH within 6 h of onset, intensive blood pressure reduction (systolic target <140 mmHg in <1 h) is safe and may be superior to a systolic target <180 mmHg. No specific agent can be recommended.	Moderate	Weak	GRADE	2014	Clinical trials	2013
KSCVS/CRCS	If the SBP is >200 mm Hg or mean arterial pressure (MAP) is >150 mm Hg, then consider aggressive blood pressure reduction with a continuous intravenous infusion of drugs, with frequent BP monitoring every 5 minutes.	III	B	KSCVS/CRCS	2014	Clinical trials and observational studies	2013
	If the SBP is >180 mm Hg or MAP is >130 mm Hg and there is any possibility of an intracranial pressure (ICP) elevation, then consider ICP monitoring and reducing blood pressure using an intermittent or continuous intravenous infusion while maintaining a cerebral perfusion pressure of 50–70 mm Hg.	III	B				
	If the SBP is >180 mm Hg or MAP is >130 mm Hg and there is no evidence of an ICP elevation, then consider a modest reduction of blood pressure using an intermittent or continuous intravenous infusion (MAP of 110 mm Hg for a blood pressure of 160/90 mm Hg) and clinically reexamine the patient every 15 minutes.	III	B				
	In patients with acute ICH, when the SBP is measured between 150 and 220 mm Hg, the SBP may be safely lowered to 140 mmHg within 1 hour.	Ib	A				

AHA/ASA: American Heart Association/American Stroke Association. ACC: American College of Cardiology. ESO: European Stroke Organization. KSCVS/CRCS: Korean Society of Cerebrovascular Surgeons. Clinical Research Center for Stroke. GRADE: the Grading of Recommendations Assessment, Development, and Evaluation.

Figure 1. Bias assessment in the included clinical trials using RoB 2.

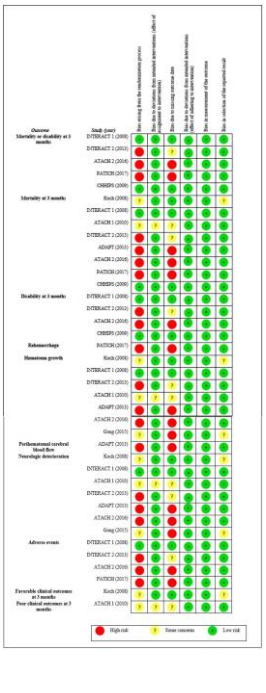

Table 2. Quality appraisal of clinical practice guidelines using the AGREE-II.

Clinical practice guideline	AGREE-II domains						
	1	2	3	4	5	6	Overall quality
AHA/ASA	100%	55.6%	72.9%	100%	81.3%	100%	66.7%
ESO	100%	66.7%	80.2%	100%	87.5%	100%	83.3%
KSCVS/CRCS	91.7%	52.8%	51%	100%	70.8%	20.8%	50%

AHA/ASA: American Heart Association/American Stroke Association. ACC: American College of Cardiology. ESO: European Stroke Organization. KSCVS/CRCS: Korean Society of Cerebrovascular Surgeons. Clinical Research Center for Stroke.

Table 3 . Main characteristics of included clinical trials.

Included study (year)	Design	Inclusion criteria (age; ICH description; blood pressure; time of onset)	Blood pressure target (intervention/control)	Pharmacological agents	Number of participants (intervention/control)	Duration of follow-up	Outcomes results
Koch (2008)	RCT	18 years of age or older; acute spontaneous supratentorial ICH; MAP >110 mmHg; within 8 h of onset	MAP <110 mmHg/MAP: 110-130 mmHg	Available BP lowering agents	42 (21/21)	3 months	**Mortality at 3 months:** RR = 0.95 (0.22-4.14) **Disability at 3 months:** RR = 1.43 (0.63-3.24) **Hematoma volume increase (mean mL±SD)*:** 2.4±6.7/2.4±5.3; p= 0.97
INTERACT 1 (2008)	RCT (open label pilot)	18 years of age or older; spontaneous ICH; SBP: 150-220 mmHg; within 6 hours of onset	SBP <140 mmHg/SBP <180 mmHg	Available BP lowering agents	404 (203/201)	3 months	**Mortality at 3 months*:**21/25; p= 0.51 **Disability at 3 months*:** 74/70, p= 0.98 **Neurological deterioration at 72 h*:** 31/30, p= 0.94 **Favorable clinical outcomes:** 131/129
CHHIPS (2009)	Pilot RCT	18 years of age or older; any type of acute stroke; SBP: 160-200 mmHg; within 36 h of onset	SBP: 145-155 mmHg/SBP >155 mmHg	Lisinopril Labetalol	179 [58 (labetalol)/ 58 (lisinopril)/63 (placebo)]	3 months	**Mortality at 3 months*:** 2 (labetalol and lisinopril/0 (placebo) **Disability at 3 months*:** 13 (labetalol and lisinopril/3 (placebo)
ATACH 1 (2010)	Non RCT	No reported restrictions for age; spontaneous ICH; SBP >170 mmHg; within 6 hours of onset	SBP: 170-200 mmHg/140-170 mmHg/110-140 mmHg	Intravenous nicardipine hydrochloride	60 (18/20/22)	3 months	**Hematoma expansion >33%:** RR = 0.67 (0.27-1.63) **Poor clinical outcomes at 3 months:** RR = 0.72 (0.37-1.39)
INTERACT 2 (2013)	RCT (open label)	18 years of age or older; spontaneous ICH; SBP: 150-220 mmHg; within 6 hours of onset	SBP <140 mmHg/SBP <180 mmHg	Available BP lowering agents	2839 (1403/1436)	3 months	**Mortality at 3 months:** RR = 1.00 (0.82-1.22) **Disability at 3 months:** RR = 0.92 (0.84-1.00) **Hematoma expansion >30%:** RR = 0.99 (0.80-1.22) **Neurological deterioration at 24 h:** RR = 0.96 (0.80-1.14) **Nonfatal serious adverse events:** RR = 0.99 (0.86-1.13)
ADAPT (2013)	RCT (open label)	18 years of age or older; spontaneous ICH; SBP ≥150 mmHg; within 24 hours of onset	SBP <150 mmHg/SBP: 150-180 mmHg	Available BP lowering agents	75 (39/36)	3 months	**Absolute hematoma increase (mean mL, IQR)*:** 0.67 (-0.08 - -3.75)/0.71 (-0.04 - 2.91) **Neurological deterioration:** RR = 1.46 (0.26-8.23)
Gong (2015)	RCT	No reported restrictions for age; spontaneous basal ganglia ICH; SBP inclusion criteria is not described; times of onset is not described	SBP: 130-140 mmHg/ SBP: 160-180 mmHg	Intravenous nitroglycerin was used in the first hour. Available BP lowering agents replaced it after 24 h.	120 (60/60)	14 days	**Hematoma volume at 24 h (mean mL±SD)*:** 11.8±6.9/0.14.7±6.7; p=0.043 **NIHSS at 14 d (mean±SD)*:** 6.28±7.82, p =0.036
ATACH 2 (2016)	RCT (open label)	18 years of age or older; spontaneous ICH; SBP >180 mmHg; within 4.5 hours of onset	SBP <140 mmHg/SBP <180 mmHg	Before randomization: available BP lowering agents were used to keep SBP between 180 and 140 mmHg. After randomization: nicardipine or other agents (labetalol, dihizares or urapidil).	1000 (500/500)	3 months	**Mortality at 3 months:** RR = 0.97 (0.60-1.57) **Disability at 3 months:** 1.01 (0.88-1.14) **Neurological deterioration at 24 h:** RR = 1.38 (0.92-2.07) **Any serious adverse events:** RR = 1.28 (0.99-1.66)
PATCH (2017)	RCT (open label)	18 years of age or older; spontaneous ICH and intraventricular extension; SBP: 150-220 mmHg; within 24 hours of onset	SBP: 140-120 mmHg/ SBP <180 mmHg	Available BP lowering agents	201 (100/101)	3 months	**Mortality or disability at 3 months:** OR = 0.66 (0.32-1.35) **Mortality at 3 months:** OR 0.89 (0.37-2.10) **Rebemorrhage:** OR = 1.16 (0.43-3.11) **Cerebral ischemia:** OR = 1.66 (0.71-3.86) **Acute renal dysfunction:** OR = 0.50 (0.02-9.10)

*Intervention/control.
Definitions:
MAP: median arterial pressure. SBP: systolic blood pressure. BP: blood pressure. RR: relative risk. OR: odds ratio. SD: standard deviation. IQR: interquartile range.
Mortality was defined as a mRS of 6 points. Disability was defined as a mRS scores of 3-5 points.
Neurological deterioration was defined as a decline of ≥2 points on the Glasgow Coma Scale or an increase of ≥4 points in the National Institute of Health Stroke Scale (NIHSS) from baseline.
Favorable clinical outcomes was defined as a mRS ≤2.
Poor clinical outcome was defined as a mRS of 4-6 points.
Any serious adverse event was defined as recurrent stroke, acute coronary event, other vascular events, neurological deterioration, renal failure, pneumonia, sepsis, fracture, hypotension, and other non-vascular events

Table 4. Main characteristics of included systematic reviews.

Author (year)	Searching date	Design of primary studies	Assessed outcomes	No. of primary studies	No. of participants[a]	Results (95% CI), effects model, heterogeneity	Main conclusions/interpretation	AMSTAR 2[b]
Tsivgoulis (2014)	February 2014	Only RCTs	3-month mortality	4	1662/1688	OR = 1.01 (0.83-1.23), random, I² = 0%	Intensive reduction appears to be safe and is associated with a potentially lower likelihood of unfavorable outcomes.	11/16
			3-month mortality and disability	4	1662/1688	OR = 0.87 (0.76-1.01), random, I² = 0%		
			Crude absolute hematoma growth	4	1662/1688	SMD = -0.11 (-0.21 - -0.01), random		
			Adjusted hematoma growth[c]	2	1602/1631	SMD = -1.33 (-3.03 - -0.04), random		
Pan (2015)	July 2014	Only RCTs	Serious adverse effects[d]	2	1602/1631	OR = 0.96 (0.82-1.13), fixed, I² = 0%	Intensive reduction is safe enough and might have a potency of reducing hematoma enlargement and improving clinical outcome.	11/16
			Hematoma growth (24 h)[e]	3	1623/1652	OR = 0.91 (0.72-1.17), fixed, I² = 41%		
			3-month mortality	4	725/702	OR = 0.97 (0.79-1.20), fixed, I² = 0%		
			3-month favorable clinical outcome[f]	3	1623/1652	OR = 1.13 (0.98-1.30), fixed, I² = 0%		
Ma (2015)	July 2013	Only RCTs	3- month mortality	5	1680/1695	OR = 0.99 (0.81-1.23), fixed, I² = 0%	Intensive reduction is probably beneficial for functional outcome, but the evidence is still insufficient.	11/16
			3-month mortality and disability	4	1641/1659	OR = 0.90 (0.78-1.03), fixed, I² = 25%		
			Neurological deterioration[g]	4	1641/1659	OR = 0.97 (0.80-1.18), fixed, p = 0.88		
			Hematoma growth	4	1641/1659	OR = 0.83 (0.61-1.11), fixed, p = 0.19		
			Hypotension	2	1602/1631	OR = 0.84 (0.36-1.96), fixed, p = 0.69		
			Cardiovascular event	2	1602/1631	OR = 0.90 (0.55-1.47), fixed, p = 0.67		
Zhang (2016)	May 2016	Only RCTs	3-month mortality	3	1618/1643	OR = 0.97 (0.79-1.20), fixed, I² = 0%	Intensive reduction neither reduce mortality and dependency at 3 months nor prevent hematoma extension, but appears to be safe.	9/16
			3-month mortality and disability	3	1606/1634	OR = 0.89 (0.77-1.02), fixed, I² = 0%		
			Hematoma growth	5	1693/1719	OR = 0.83 (0.49-1.41), random, I² = 65%		
			Early neurological deterioration (24-72 h)	4	1632/1653	OR = 0.97 (0.80-1.18), fixed, I² = 0%		
Boulouis (2017)	June 2016	Only RCTs	3-month mortality[h]	5	2145/2170	OR = 0.99 (0.82-1.20), random, I² = 0%	Intensive reduction is safe, but does not seem to provide an incremental clinical benefit. Safety is not clear in patients with large hematoma and increased intracranial pressure.	9/16
			3-month mortality and disability[h]	5	2145/2170	OR = 0.91 (0.81-1.03), random, I² = 0%		
			Hematoma growth (24 h)[h]	5	1173/1128	OR = 0.82 (0.68-1.00), random, I² = 1.7%		
			Severe adverse events	2	703/701	OR = 1.23 (0.90-1.69), random, I² = 27.2%		
Lattanzi (2017)	June 2016	Only RCTs	3-month mortality	5	2122/2147	RR = 0.99 (0.83-1.17), fixed, I² = 0%	Intensive reduction is overall safe and attenuated the hematoma expansion, but fails to improve clinical outcomes.	10/16
			3-month mortality and disability	4	2082/2105	RR = 0.96 (0.91-1.01), fixed, I² = 0%		
			Absolute hematoma growth (24 h; mL)	3	686/666	WMD = -1.53 (-2.94 - -0.12), fixed, I² = 0%		
			Early neurological deterioration (24-72 h)	5	2130/2130	RR = 1.03 (0.88-1.20), fixed, I² 10%		
			Hematoma growth (24 h)	5	1173/1128	RR = 0.86 (0.74-1.00), fixed, I² = 2.2%		
			Hypotension (72 h)	2	703/701	RR = 1.56 (0.61-4.00), fixed, I² = 0%		
			Severe hypotension (72 h)	2	1602/1631	RR = 0.84 (0.37-1.94), fixed, I² = 0%		
			3-month any serious adverse events	3	2102/2131	RR = 1.05 (0.94-1.17), fixed, I² = 47.2%		
			Recurrent stroke (ischemic or hemorrhagic)	2	1602/1631	RR = 0.95 (0.46-1.96), fixed, I² = 0%		
			Acute coronary events	3	2102/2131	RR = 1.13 (0.45-2.85), fixed, I² = 0%		
			Renal failure	2	703/701	RR = 2.18 (1.08-4.41), fixed, I² = 0%		
Carandini (2018)	October 2016	Only RCTs	3-month mortality	6	2140/2154	RR = 0.99 (0.83-1.17), random, I² = 0%	No evidence that intensive reduction is better than standard reduction in the assessed outcome.	10/16
			3-month disability	5	2100/2112	RR = 0.96 (0.80-1.03), random, I² = 4%		
			3-month mortality and disability	5	2100/2112	RR = 0.97 (0.90-1.03), random, I² = 9%		
			Early neurological deterioration (24-72 h)	5	2130/2153	RR = 1.03 (0.88-1.19), random, I² = 0%		
			Hematoma growth (24 h)	4	1136/1092	RR = 0.83 (0.70-1.03), random, I² = 25%		
			3-month non-fatal serious adverse events[i]	3	2083/2111	RR = 1.07 (0.90-1.28), random, I² = 47%		

[a] Intervention/control
[b] Total "yes" answers
[c] It was adjusted for prognostic variables (baseline hematoma volume, hematoma location, time from onset to brain computerized tomography.
[d] It was defined as ischemic or undifferentiated stroke, acute coronary event, severe hypotension, or others according to the INTERACT trials
[e] Hematoma growth was defined as an increase of at least 30% in hematoma volume.
[f] It was defined as a mRS ≤2 points.
[g] Neurological deterioration was defined as a decrease from baseline of 2 or more points in GCS or an increase of 4 or more points in NIHSS.
[h] Authors performed a subgroup analysis of large RCTs and small RCTs (<100 patients). The presented result is the overall.
[i] It include events that were life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, or resulted in disability or a medical or surgical intervention.