EMPoweRx conference

A conference that is for us and by us

How Low Can You Go?

Blood Pressure Management in ICH

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Disclosures

- **Nothing to disclose**

Objectives

- Summarize the consequences of blood pressure (BP) derangements in the setting of spontaneous intracerebral hemorrhage (sICH)
- Review the clinical literature regarding BP management in sICH
- Develop a treatment plan for a patient who presents to the ED with sICH

Patient case:

ZA is a 72 year old male presenting with confusion, nausea/vomiting, ataxia, and GCS 12

PMH - hypertension

Home medications - amlodipine (wife states non-compliance)

BP 195/95 mmHg HR 72 bpm O2sat 98%

sICH Epidemiology & Risk Factors

- ~10% of the 795,000 strokes per year in the United States are spontaneous intracerebral hemorrhages (sICH)
  - Brain injury: Acute blood extravasation into the brain parenchyma from a ruptured cerebral blood vessel
- ICH early mortality 30-40%
- Associated causes
  - Hypertension
    - Strongest attributable risk factor
  - Cerebral amyloid angiopathy
  - Anticoagulation

Greenberg SM, et al. Stroke. 2022 Jul;53(7):e282-e361
Sheth KN. N Engl J Med. 2022 Oct 27;387(17):1589-1596.

sICH Epidemiology & Risk Factors

- Medications
  - All antithrombotics
  - NSAIDs
  - Vasoconstrictive agents
    - Triptans, SSRIs, decongestants, stimulants, phentermine, sympathomimetic drugs
  - Antihypertensives (marker of chronic HTN)
  - Estrogen containing oral contraceptives
- Substance use
  - Smoking, alcohol, marijuana, sympathomimetics

Greenberg SM, et al. Stroke. 2022 Jul;53(7):e282-e361
Sheth KN. N Engl J Med. 2022 Oct 27;387(17):1589-1596.

Clinical Presentation of sICH

- Similar to other origins of stroke
- Differentiations from ischemic
  - Headache, nausea or vomiting, depressed level of consciousness

Greenberg SM, et al. Stroke. 2022 Jul;53(7):e282-e361
Sheth KN. N Engl J Med. 2022 Oct 27;387(17):1589-1596.

Pathophysiology of sICH

- Occurs deep in brain structures
  - Small cerebral blood vessel wall damage
  - Branches of large vessels of the circle of Willis
    - Supply the basal ganglia, thalamus, pons, and deep portions of the cerebellum
- Putaminal and thalamic hemorrhages
  - Hyalinization and lipid deposits in the vessel walls → rupture
- Lobar hemorrhages
  - Chronic hypertension, anticoagulation

Greenberg SM, et al. Stroke. 2022 Jul;53(7):e282-e361
Sheth KN. N Engl J Med. 2022 Oct 27;387(17):1589-1596.

Pathophysiology of sICH

Stroke causes transient/permanent damage to the brain regulation of BP

Direct injury to brain regions and indirect effects of reduced parasympathetic activity

Increased sympathoadrenal tone, release of renin and vasoconstriction of arterioles

Impaired cardiac baroreceptor sensitivity

- Acute hypertensive response to sICH
  - Hypertension will occur in the setting of reduced cerebral perfusion pressure → increased hypertensive response is associated with hematoma expansion

Qureshi AI. Circulation. 2008 Jul 8;118(2):176-87.
Qureshi AI, et al. J Cereb Blood Flow Metab. 2018 Sep;38(9):1551-1563.

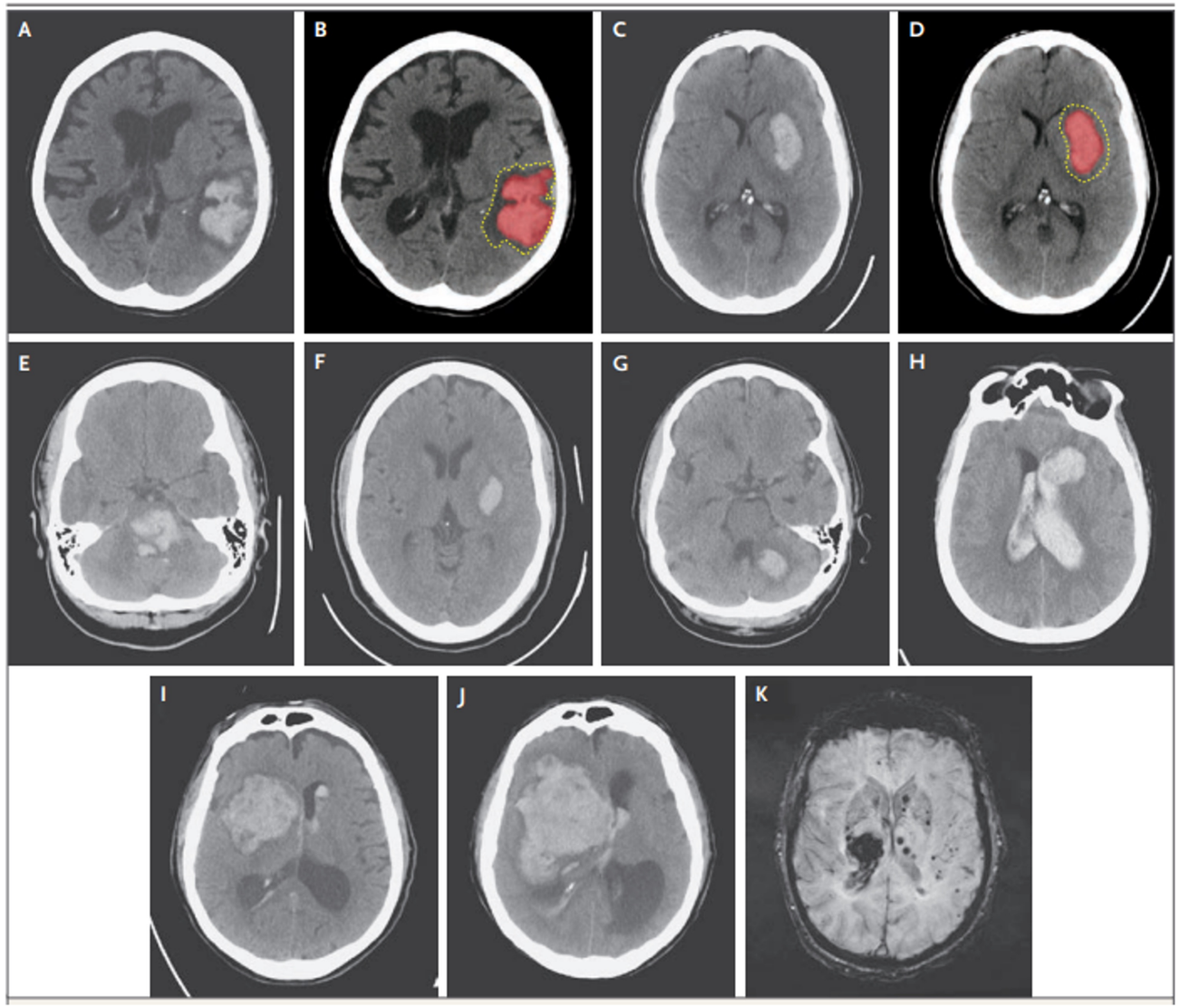


Figure 1 - Spontaneous ICH

- A-J noncontrast CT & K MRI
- A&B - Lobar intracerebral hemorrhage
- C&D - Putaminal intracerebral hemorrhage
- E - Pontine intracerebral hemorrhage in the middle portion of the brain stem
- F - Basal ganglia intracerebral hemorrhage
- G - Intracerebral hemorrhage in the left cerebellum
- H - frontal intracerebral hemorrhage with extension into the ventricles (compartments that contain cerebrospinal fluid), often referred to as an intraventricular hemorrhage
- I&J - an initial intracerebral hemorrhage that originated in the basal ganglia but underwent considerable expansion of the hematoma in the first hours after presentation
- K - an intracerebral hemorrhage in the right thalamus

Sheth KN. Spontaneous Intracerebral Hemorrhage. N Engl J Med. 2022 Oct 27;387(17):1589-1596.

Hematoma Expansion

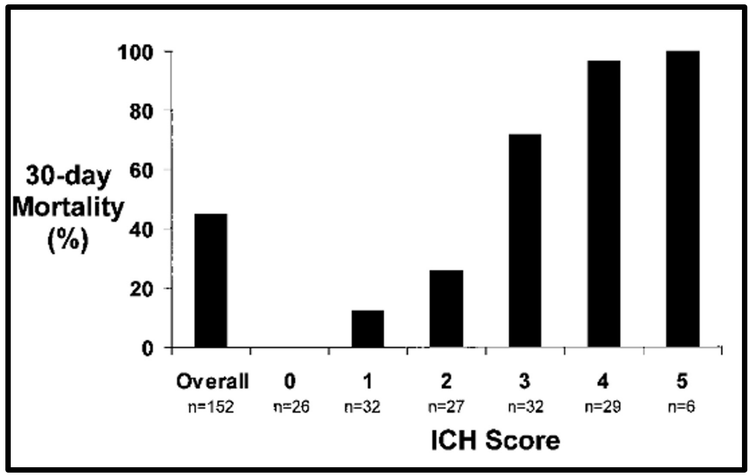
- Predictor of clinical outcomes at 3 months
- Increased volume occurs in 25% of sICH and 30-40% in those associated with anticoagulation
- Secondary brain injury
  - Occurs immediately
    - Tissue injury and surrounding edema

Sheth KN. Spontaneous Intracerebral Hemorrhage. N Engl J Med. 2022 Oct 27;387(17):1589-1596.

Patient Assessment Tools

- **ICH Score**
  - Clinical severity
  - Estimates the functional outcomes, risk of death, early and at 12 months

Component	ICH Score Points
GCS score	
3–4	2
5–12	1
13–15	0
ICH volume, cm^3	
≥30	1
<30	0
IVH	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age, y	
≥80	1
<80	0
Total ICH Score	0–6



Stroke. 2001 Apr;32(4):891-7.

Treatment Goals of sICH

- Prevention of secondary brain injury
  - Hematoma enlargement
  - Secondary cerebral edema

- Anticoagulation & antiplatelet reversal as appropriate
- Cerebral edema mamagent
- Blood pressure management

Patient case:

ZA is a 72 year old male presenting with confusion, nausea/vomiting, ataxia, and GCS 12

CT head - ICH in cerebellar region

BP 195/95 mmHg HR 72 bpm O2sat 98%

Stroke

AHA/ASA GUIDELINE

2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

Endorsed by the Society of Vascular and Interventional Neurology

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the Neurocritical Care Society

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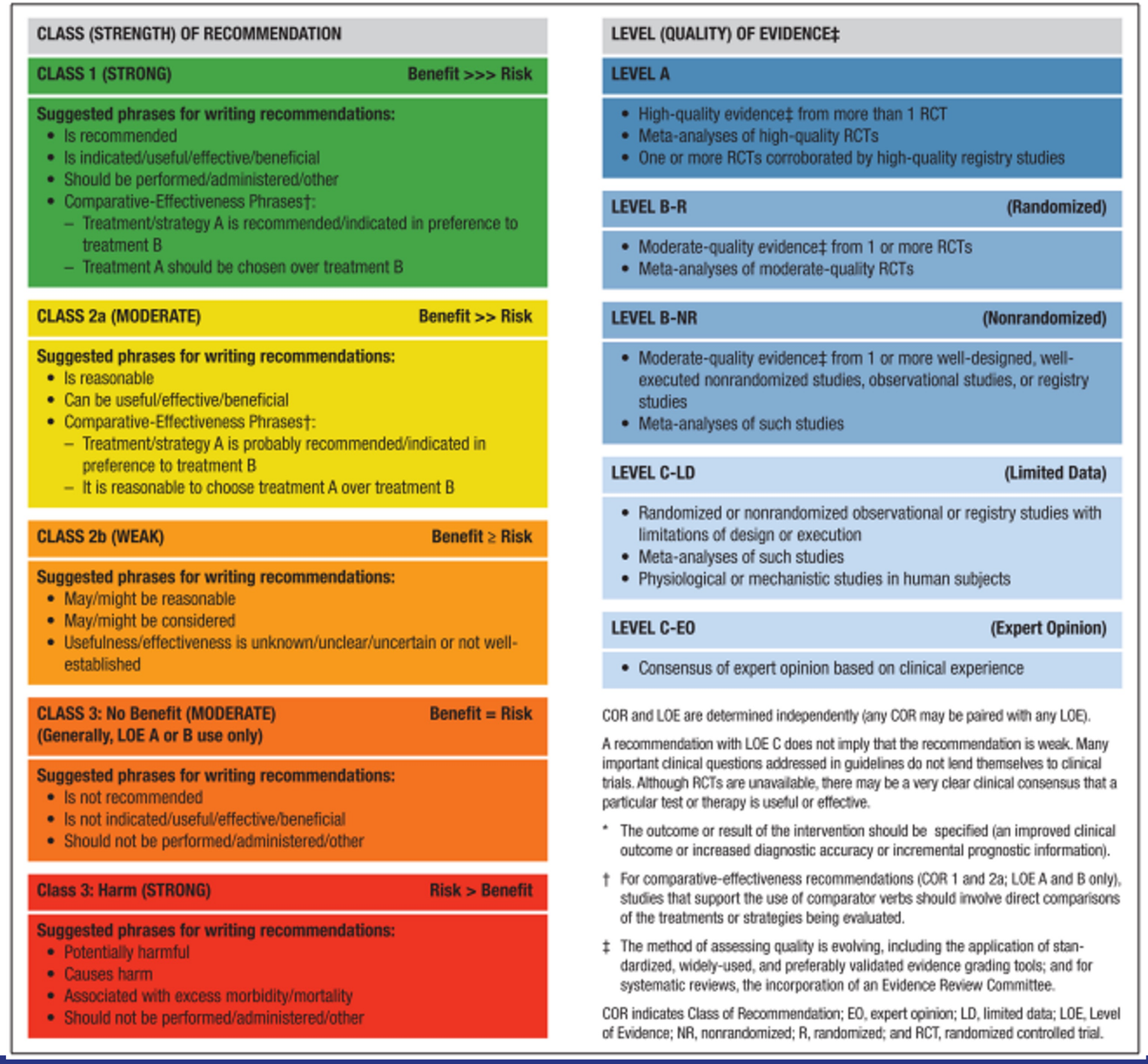
Greenberg SM, et al. Stroke. 2022 Jul;53(7):e282-e361.



CLASS (STRENGTH) OF RECOMMENDATION

CLASS 1 (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS 2a (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS 2b (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well-established

CLASS 3: No Benefit (MODERATE) — **Benefit = Risk**
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

Class 3: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R — **(Randomized)**
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR — **(Nonrandomized)**
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD — **(Limited Data)**
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO — **(Expert Opinion)**
- Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Greenberg SM, et al. Stroke. 2022 Jul;53(7):e282-e361.

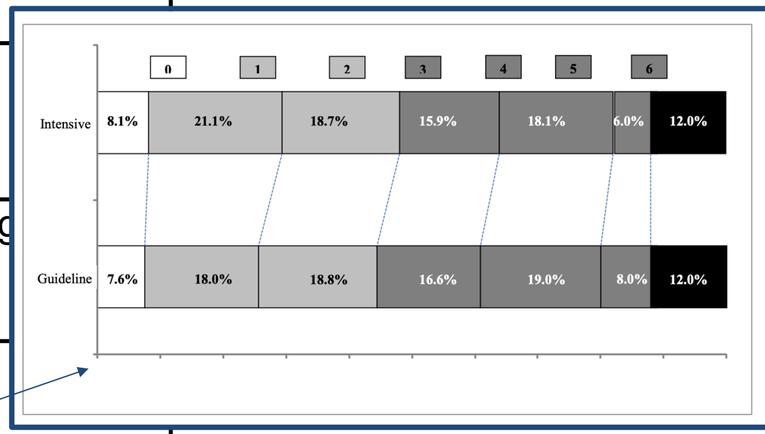
AHA/ASA 2022 Guideline Updates

Recommendations for Acute BP Lowering		
Class of recommendation	**Level of evidence**	**Recommendations**
2a	B-NR	In patients with spontaneous ICH requiring acute BP lowering, careful titration to ensure **continuous smooth and sustained control of BP,** avoiding peaks and large variability in SBP, can be beneficial for improving functional outcomes.
2a	C-LD	In patients with spontaneous ICH in whom acute BP lowering is considered, **initiating treatment within 2 hours of ICH onset** and reaching target within 1 hour can be beneficial to reduce the risk of HE and improve functional outcome
2b	B-R	In patients with spontaneous ICH of mild to moderate severity **presenting with SBP between 150 and 220** mmHg, acute lowering of SBP to a **target of 140 mmHg with the goal of maintaining in the range of 130 to 150 mmHg** is safe and may be reasonable for improving functional outcomes
2b	C-LD	In patients with spontaneous ICH presenting with **large or severe ICH or those requiring surgical decompression**, the safety and efficacy of intensive BP lowering are **not well established**
3: HARM	B-R	In patients with spontaneous ICH of mild to moderate severity **presenting with SBP >150 mmHg**, acute **lowering of SBP to <130 mmHg is potentially harmful**

Greenberg SM, et al. Stroke. 2022 Jul;53(7):e282-e361.

INTERACT 2

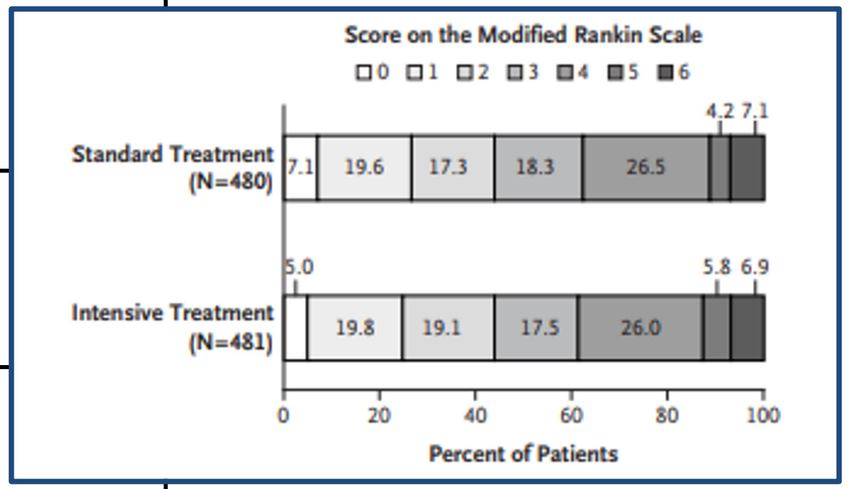
Design	International, multicenter, prospective, randomized, open-treatment, blinded end-point trial (2839 patients)
Inclusion	sICH with SBP 150-220 mmHg without contraindication to BP-lowering treatment ● Treatment within 6 hours of onset *Exclusions: structural cerebral cause of ICH, GCS 2-5, massive hematoma with poor prognosis, or if early surgery to evacuate hematoma planned*
Intervention	Intensive-treatment: SBP <140 within 1 hour after randomization Standard-treatment: Treatment to be administered if SBP >180 mmHg
Results (Mean SBP)	Intensive-treatment: 150 mm Hg (33.4% achieved goal of SBP <140 mmHg Standard-treatment: 164 mmHg
Results (Disability and Death)	No difference in rates of major disability and death between intensive and standard-treatment group (52.0% vs 55.6%, P=0.06) ● Lower modified Rankin score with intensive treatment (OR for greater disability, 0.89; P=0.04)
Conclusion	Intensive lowering of BP did not result in significant reduction in rate of death or severe disability (primary outcome) ● Better functional outcomes with intensive-treatment (mean SBP 150 mm Hg)



Anderson CS, et al. N Engl J Med. 2013;368(25):2355-65.

ATACH-2

Design	International, randomized, multicenter, two-group, open-label trial
Inclusion	sICH (supratentorial) with one SBP ≥180 mmHg ● Treatment within 4.5 hours after symptom onset *Exclusions: SBP reduced to <140 mmHg before randomization, GCS <5*
Intervention	Intensive-treatment: SBP 110-139 mmHg for 24 hours after randomization Standard-treatment: 140-179 mmHg for 24 hours after randomization
Results: Mean SBP	Intensive-treatment: 128.9 ±16 mmHg (treatment failure in 12.2% of patients) Standard-treatment: 141.1 ± 14.8 mmHg
Results: Disability and Death	No difference in rates of death or disability between intensive and standard-treatment (38.7% vs 37.7%, P=0.85) ● **Rate of renal adverse events within 7 days after randomization significantly higher in intensive vs standard-treatment group (9.0% vs 4.0%, P=0.002)**
Conclusion	Treatment to achieve SBP 110-139 mmHg did not result in lower rate of death or disability than standard reduction to target 140-179 mmHg ● More renal adverse effects with intensive-treatment



Qureshi AI, et al. N Engl J Med. 2016;375(11):1033-43.

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Greenberg SM, et al. Stroke. 2022 Jul;53(7):e282-e361.

Blood Pressure Variability in sICH

- **Pooled analyses INTERACT2 and ATATCH-2**
  - Achieving early and stable systolic blood pressure seems to be safe and associated with favourable outcomes (functional status) in patients with acute ICH of predominantly mild-to-moderate severity
- **Retrospective data**
  - Higher systolic blood pressure variability in the first 24 hours of admission
    - Associated with unfavorable in-hospital outcome (mRS 4-6) among ICH patients

Divani AA, et al. Stroke. 2019 Aug;50(8):2023-2029.
Moullaali TJ, et al. Lancet Neurol. 2019 Sep;18(9):857-864.

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Greenberg SM, et al. Stroke. 2022 Jul;53(7):e282-e361.

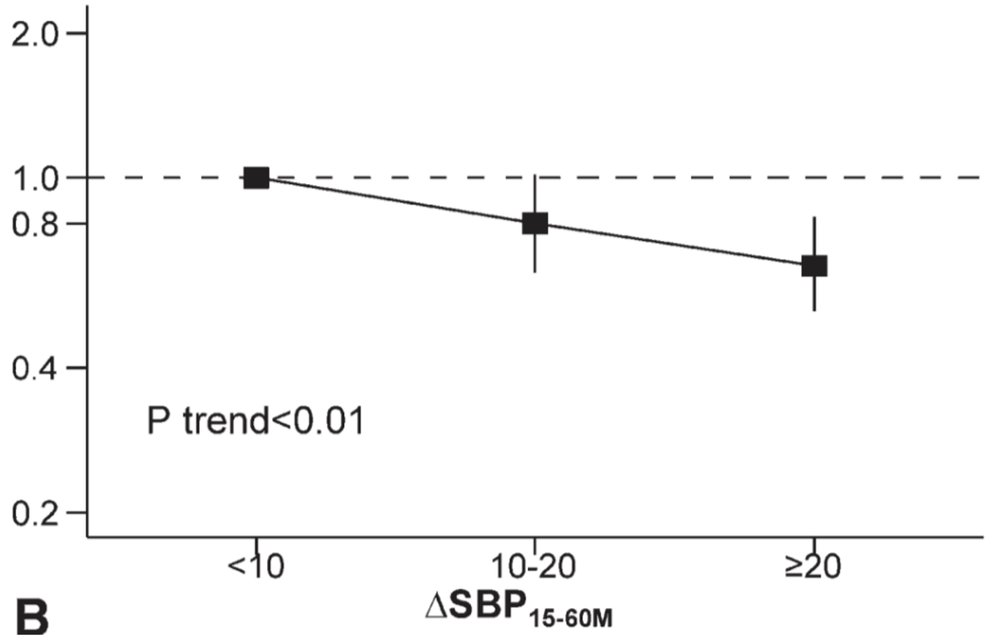
Timing of BP Management

- **Post-hoc analysis of ATACH-2**
  - 354 (38.7%) received nicardipine within 2 hours intensive vs standard

Association of Ultra-Early (≤2 hour) Intensive Blood Pressure Treatment and Outcomes

	Unadjusted analysis		Adjusted analysis[a]	
Outcome	**Relative risk (95% CI)**	***p***	**Relative risk (95% CI)**	***p***
Hematoma growth	0.56 (0.34–0.93)	0.024	0.56 (0.34–0.92)	0.022
Functional independence	1.86 (1.19–2.91)	0.007	2.17 (1.28–3.68)	0.004
Good outcome	1.48 (0.97–2.26)	0.072	1.68 (1.01–2.83)	0.048
Death	0.64 (0.28–1.46)	0.29	0.62 (0.27–2.12)	0.600

- **Post-hoc analysis of INTERACT2**
  - Odds ratio of death or major disability



Li Q, et al. Ann Neurol. 2020 Aug;88(2):388-395.
Wang X, et al. Hypertension. 2015;65:1026–1032.

Patient case:

ZA is a 72 year old male presenting with confusion, nausea/vomiting, ataxia, and GCS 12

CT head - ICH in cerebellar region

BP 195/95 mmHg HR 72 bpm O2s

How do you want to treat this patient?

IV Dihydropyridine CCB Options

Agent	Onset	Peak	Duration
Nicardipine	Within minu		1-2 hours (up to 6 hours)
Clevidipine	2 to 4	ined	5 to 15 minutes

Clinical Controversy!

Dosing Strategies

- **Clevidipine**
  - Continuous IV infusion: Initial: 1 to 2 mg/hour.
    - *Titration:* Initial: Dose may be doubled at **90-second intervals** toward BP goal. As BP approaches goal, increase dose by smaller increments every ~5 to 10 minutes. **Note:** For every 1 to 2 mg/hour increase in dose, an approximate reduction of 2 to 4 mm Hg in systolic BP may occur.
    - *Usual maintenance:* 4 to 6 mg/hour; maximum: 21 mg/hour (1,000 mL per 24 hours due to lipid load restriction). Most patients will require doses ≤16 mg/hour. In patients with severe hypertension, doses up to 32 mg/hour may be considered based on limited short-term experience. Data are limited beyond 72 hours.

- **Nicardipine**
  - Continuous IV infusion: Initiate 5 mg/hour; titrate by 2.5 mg/hour at **5- to 15-minute intervals** (maximum dose: 15 mg/hour). When goal BP is obtained, adjust dose to maintain proper BP limits.

What agent do you have on formulary?

neurocritical care society Neurocrit Care (2017) 26:167–173
DOI 10.1007/s12028-016-0349-4

ORIGINAL ARTICLE

Clevidipine Versus Nicardipine for Acute Blood Pressure Reduction in a Neuroscience Intensive Care Population

Jacqueline R. Finger[1] · Lisa M. Kurczewski[2] · Gretchen M. Brophy[3]

- Purpose
  - The purpose of this study was to compare the difference in time to achieve target systolic blood pressure (SBP) goals with clevidipine versus nicardipine infusions in patients admitted to the neuroscience intensive care unit (NSICU)
- Methods
  - A retrospective review
  - Patients receiving clevidipine or nicardipine infusions while in the NSICU between July 1, 2011 and June 30, 2014
  - Patients were matched based on indication for BP lowering and target SBP
  - Primary endpoints
    - Time to target SBP and percentage of time within target BP range

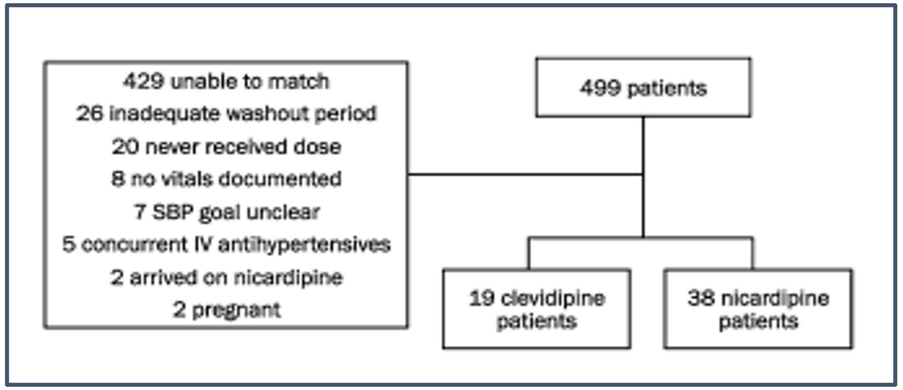
Finger JR, et al. Neurocrit Care. 2017 Apr;26(2):167-173.

Clevidipine Versus Nicardipine for Acute Blood Pressure Reduction in a Neuroscience Intensive Care Population

	Clevidipine (n = 19)	Nicardipine (n = 38)
Age (yrs) [median (IQR)]	61 (57–73)	56 (47–66)
Sex [n (%)]		
Male	12 (63.2)	20 (52.6)
Female	7 (36.8)	18 (47.4)
Weight (kg) [median (IQR)]	93 (77–106)	90 (76–101)
Indication [n (%)]		
ICH	8 (42.1)	16 (42.1)
Ischemic stroke	2 (10.5)	4 (10.5)
Other[a]	9 (47.4)	18 (47.4)
Target SBP (mmHg) [n (%)]		
<180	2 (10.5)	4 (10.5)
<160	11 (57.9)	22 (57.9)
<150	2 (10.5)	4 (10.5)
<140	4 (21.1)	8 (21.1)
Ordering physician service		
Neurosurgery	6 (31.6)	23 (60.5)
Neurology	4 (21.1)	8 (21.1)
Intensivist	9 (47.4)	2 (5.3)
Emergency department	0	5 (13.2)

ICH intracerebral hemorrhage, *SBP* systolic blood pressure

[a] Includes tumor resection, encephalopathy, hydrocephalus, seizure, cerebral edema, ventriculoperitoneal shunt removal, transient ischemic attack, and elective procedures



Finger JR, et al. Neurocrit Care. 2017 Apr;26(2):167-173.

Clevidipine Versus Nicardipine for Acute Blood Pressure Reduction in a Neuroscience Intensive Care Population

Table 2 Endpoint comparisons of clevidipine versus nicardipine

	Clevidipine ($n = 19$)	Nicardipine ($n = 38$)	p
Primary endpoints			
Time to target SBP (min) [median (IQR)][a]	30 (21–65)	46 (30–126)	0.13
Percentage of time in target SBP range [median (IQR)]	79 (67–92)	78 (61–92)	0.64
Secondary endpoints			
SBP[b] (mmHg) [median (IQR)]	145 (141–151)	146 (138–153)	0.92
Dose[c] (mg/h) [median (IQR)]	3 (1.5–8)	5 (4–7)	0.13
Max dose (mg/h) [median (IQR)]	5.3 (3–10)	8.5 (5–10.3)	0.18
Infusion time (h) [median (IQR)]	23 (9.7–67)	13.5 (6.3–26.1)	0.07
Rescue antihypertensive medications given during infusion [n (%)]	8 (42.1)	15 (39.5)	0.8
Total volume of administration (mL) [mean (SD)]	530 (750)	1254 (1803)	0.02
Safety endpoints			
SBP $<$ 100 mmHg [n (%)]	3 (15.8)	3 (7.9)	0.4
HR $>$ 120 bpm [n (%)]	4 (21.1)	4 (10.5)	0.4

[a] Clevidipine $n = 17$, nicardipine $n = 32$

[b] Average SBP was calculated for each patient for this analysis

[c] Median dose was calculated for each patient for this analysis

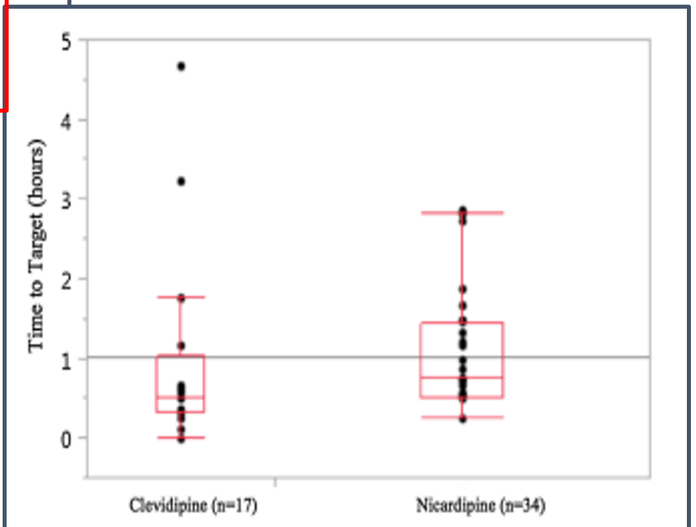


Fig. 2 Time to target SBP

Finger JR, et al. Neurocrit Care. 2017 Apr;26(2):167-173.

Comparison of Nicardipine with Clevidipine in the Management of Hypertension in Acute Cerebrovascular Diseases

Zachary Rosenfeldt, PharmD,* Katelyn Conklen, PharmD,† Breck Jones, MD,‡
Don Ferrill, PharmD,† Maithili Deshpande, PharmD,§ and Fazeel M. Siddiqui, MD‡

- Purpose
  - To compare the efficacy and safety of nicardipine and clevidipine in acute stroke
- Methods
  - Retrospective review compared nicardipine with clevidipine for hypertension in acute stroke patients from March 17, 2015 to December 23, 2016
  - Ischemic and hemorrhagic stroke types were evaluated
  - Patients were excluded if under 18 years, had traumatic brain injury, had intracranial neoplasm, were on dialysis, had both study drugs during the stroke admission, or the study drug was infused for less than 1 hour
- Efficacy outcomes were: time to goal blood pressure, percent time in goal, blood pressure range, and need for additional antihypertensive agents during the infusion.

Rosenfeldt Z, et al. J Stroke Cerebrovasc Dis. 2018 Aug;27(8):2067-2073.

Comparison of Nicardipine with Clevidipine in the Management of Hypertension in Acute Cerebrovascular Diseases

Patient Characteristics	Overall sample (N = 119)	Nicardipine (n = 60)	Clevidipine (n = 59)	*P* Value
Stroke type†, (n [%])	56 (47.1)	27 (45.0)	29 (49.2)	.07
Intracerebral hemorrhage				
Ischemic stroke	37 (31.1)	24 (40.0)	13 (22.0)	
Nontraumatic extradural hemorrhage	1 (.84)	1 (1.7)	0 (.0)	
Subarachnoid hemorrhage	20 (16.8)	7 (11.7)	13 (22.0)	
Subdural hemorrhage	5 (4.2)	1 (1.7)	4 (6.8)	
Target SBP†, (n [%])	73 (61.3)	30 (50.0)	43 (72.9)	.07
<140 mm Hg				
<180 mm Hg	17 (14.3)	10 (16.7)	7 (11.9)	
<185 mm Hg	6 (5.0)	4 (6.7)	2 (3.4)	

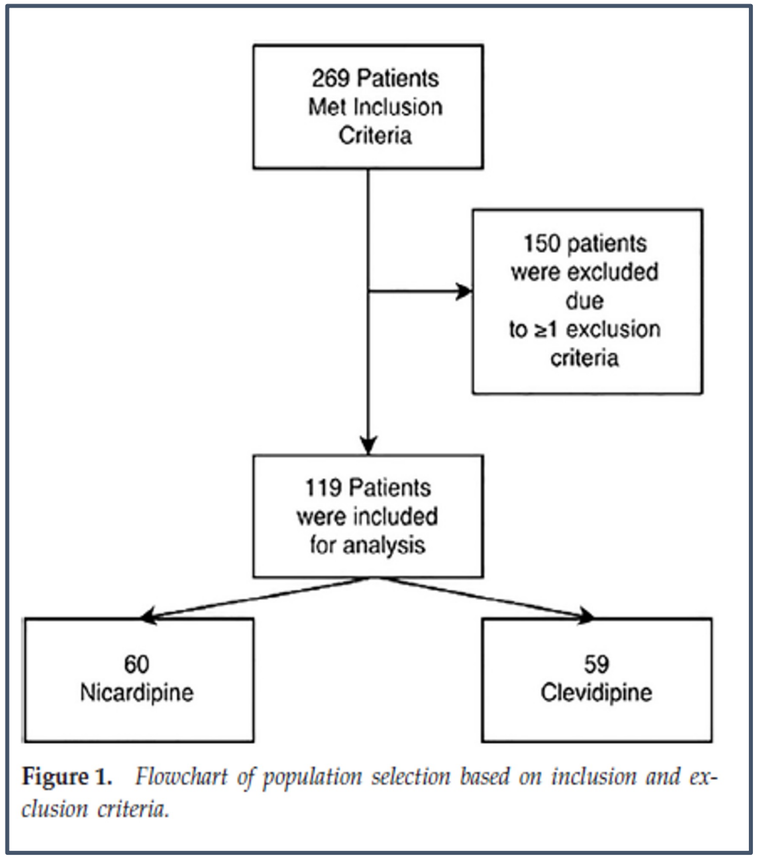


Figure 1. *Flowchart of population selection based on inclusion and exclusion criteria.*

Rosenfeldt Z, et al. J Stroke Cerebrovasc Dis. 2018 Aug;27(8):2067-2073.

Comparison of Nicardipine with Clevidipine in the Management of Hypertension in Acute Cerebrovascular Diseases

Table 2. *Outcome distribution*

Outcomes	Nicardipine (n = 60)	Clevidipine (n = 59)	*P* Value
Systolic goal reached in 1 h†, (n [%])	44 (73.3)	39 (66.1)	.39
Yes			
No	16 (26.7)	20 (33.9)	
Systolic goal reached in 6 h†, (n [%])	57 (95.0)	58 (98.3)	.62
Yes			
No	3 (5.0)	1 (1.7)	
Composite outcome†, (n [%])	23 (43.3)	30 (50.9)	.41
Yes			
No	34 (56.7)	29 (49.2)	
ICU length of stay* (d), mean (SD)	5.4 (6.2)	7.8 (6.5)	.015
ICU length of stay (IQR)	4	11	
Hospital length of stay*(d), mean (SD)	10.7 (9.2)	12.1 (7.9)	.17
Hospital length of stay (IQR)	8.5	12	
Time to goal SBP*(min), mean (SD)	65.5 (108.2)	65.8 (101.0)	.83
Time spent in goal SBP*(min), mean (SD)	1078.1 (1174.5)	1789.9 (2300.7)	.06
Max SBP during infusion (mm Hg)*, mean (SD)	174.3 (25.8)	173.6 (23.3)	.87
Min SBP during treatment (mm Hg)*, mean (SD)	113.1 (16.9)	109.1 (14.2)	.17
SBP range*(mm Hg)	61.1 (26.8)	64.3 (27.7)	.52
Additional IV antihypertensives used per min, mean (SD)	.0014 (.0005)	.0013 (.0002)	.21

Rosenfeldt Z, et al. J Stroke Cerebrovasc Dis. 2018 Aug;27(8):2067-2073.

Original Research

Comparison of Clevidipine and Nicardipine for Acute Blood Pressure Reduction in Patients With Stroke

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- Purpose
  - To determine whether clevidipine (CLEV) achieved faster blood pressure control compared to nicardipine (NIC) in patients presenting with either an acute ischemic stroke (AIS) or a spontaneous intracerebral hemorrhage (ICH)
- Methods
  - Retrospective, observational, cohort study conducted in patients with AIS or ICH admitted to the emergency department of a Comprehensive Stroke Center from November 2011 to June 2013 who received CLEV or NIC continuous infusion for acute blood pressure management

Allison TA, et al. J Intensive Care Med. 2019 Nov-Dec;34(11-12):990-995.

Comparison of Clevidipine and Nicardipine for Acute Blood Pressure Reduction in Patients With Stroke

Treatment

- Clevidipine titration used a starting rate of 2 mg/h, which was then increased by doubling the dose every 90 seconds until a rate of 12 mg/h was reached, and then increasing by 4 mg/h increments to a maximum dose of 32 mg/h. Nicardipine was initially started at 5 mg/h and titrated by nursing discretion **every 15 minutes** to a maximum dose of 15 mg/h.

Table 1. Patient Demographics.

	Clevidipine (n = 70)	Nicardipine (n = 140)	*P* Value
Male, n (%)	39 (56)	79 (56)	.922
Age, mean (SD), years	63.1 (15.4)	62.2 (14.2)	.588
Race, n (%)			.084
Caucasian	13 (18.6)	35 (25)	
Black	16 (22.9)	43 (30.7)	
Hispanic	9 (12.9)	23 (16.4)	
Asian	1 (1.4)	4 (2.9)	
Other	31 (44.2)	35 (25)	
Diagnosis, n (%)			.001
AIS	37 (52.9)	40 (28.6)	
ICH	33 (47.1)	100 (71.4)	
Admission GCS, median (IQR)	14 (9-15)	12 (7-15)	.057
Admission NIHSS, median (IQR)	12 (6-22.5)	14 (5-25)	.922
Admission SBP, mean (SD)	200.3 (32)	190.2 (35.6)	.046
Medical history, n (%)			
Coronary artery disease	7 (10)	19 (13.6)	.459
Previous MI	2 (2.9)	4 (2.9)	1.000
Hypertension	62 (88.6)	103 (73.6)	.013
Congestive heart failure	4 (5.7)	5 (3.6)	.471
Previous stroke	20 (28.6)	26 (18.6)	.099
Atrial fibrillation	9 (12.6)	9 (6.5)	.117

Abbreviations: AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; IQR, interquartile range; GCS, Glasgow Coma Scale; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; SD, standard deviation.

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Comparison of Clevidipine and Nicardipine for Acute Blood Pressure Reduction in Patients With Stroke

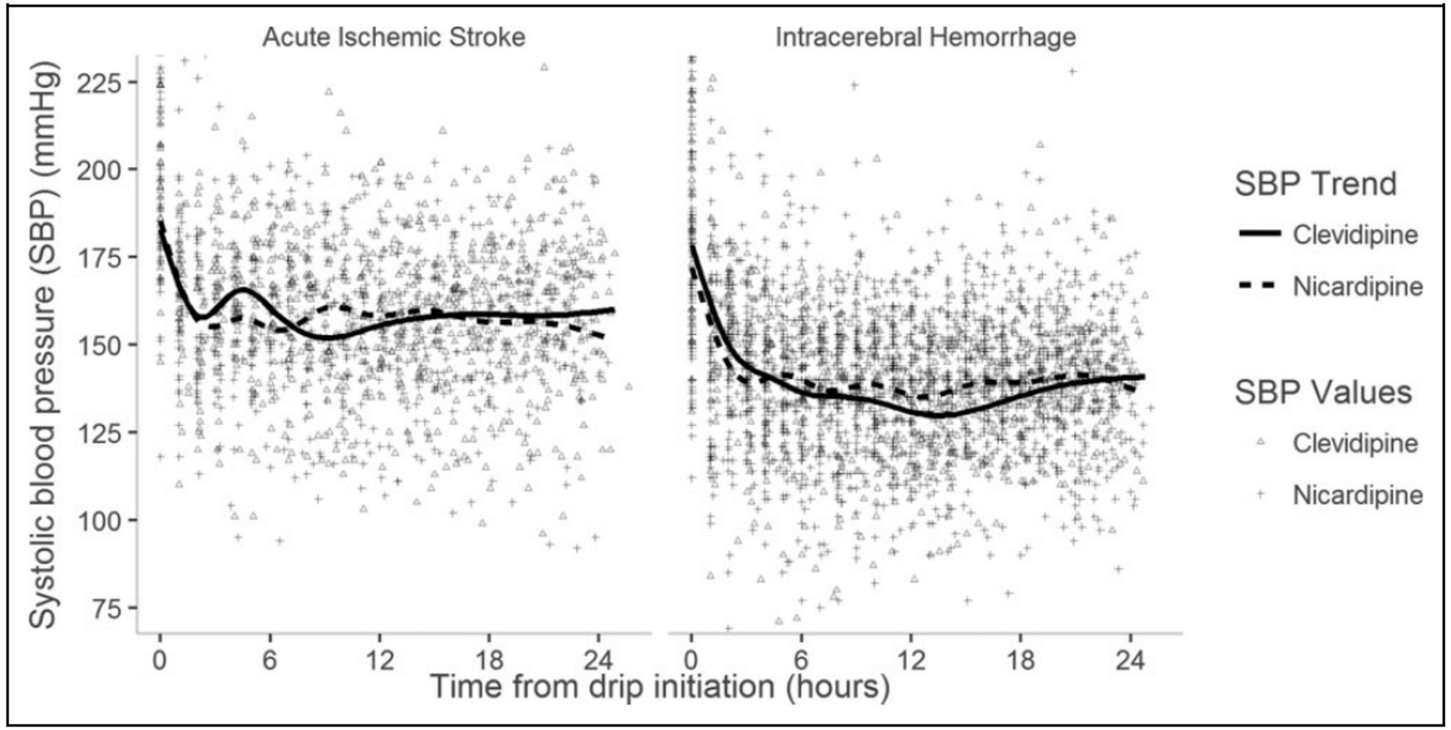

Table 2. SBP Responses Within First 24 Hours From Time of Continuous Infusion Initiation.[a]

	Clevidipine	Nicardipine	*P* Value
All patients	n = 70	n = 140	
Initial SBP (mm Hg)	199 (31)	184 (34)	.002
Final SBP (mm Hg)	150 (23)	142 (24)	.020
Percent change between initial and final SBP (%)	−23 (17)	−21 (19)	.387
Percent time below SBP goal (%)	80 (19)	75 (19)	.059
SBP change at 2 hours (mm Hg)	−43 (36)	−32 (34)	.031
SBP percent change at 2 hours (mm Hg)	−20 (16)	−16 (16)	.058
24-hour mean SBP (time weighted; mm Hg)	150 (15)	146 (13)	.041
Acute ischemic stroke	n = 37	n = 40	
Initial SBP (mm Hg)	202 (28)	193 (30)	.198
Final SBP (mm Hg)	157 (22)	157 (24)	.955
Percent change between initial and final SBP (%)	−21 (14)	−17 (21)	.280
Percent time below SBP goal (%)	89 (12)	87 (16)	.730
SBP change at 2 hours (mm Hg)	−43 (34)	−30 (37)	.123
SBP percent change at 2 hours (mm Hg)	−20 (14)	−14 (19)	.094
24-hour mean SBP (time-weighted; mm Hg)	160 (11)	158 (14)	.610
Intracerebral hemorrhage	n = 33	n = 100	
Initial SBP (mm Hg)	197 (34)	181 (35)	.021
Final SBP (mm Hg)	141 (20)	135 (21)	.165
Percent change between initial and final SBP (%)	−26 (19)	−23 (18)	.406
Percent time below SBP goal (%)	71 (21)	70 (17)	.832
SBP change at 2 hours (mm Hg)	−43 (38)	−33 (32)	.130
SBP percent change at 2 hours (mm Hg)	−20 (18)	−16 (15)	.261
24-hour mean SBP (time-weighted; mm Hg)	139 (10)	141 (9)	.335

Abbreviation: SBP, systolic blood pressure.
[a]All values reported as mean (standard deviation).

Allison TA, et al. J Intensive Care Med. 2019 Nov-Dec;34(11-12):990-995.

Neurocrit Care
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ORIGINAL WORK

Comparison of Intravenous Antihypertensives on Blood Pressure Control in Acute Neurovascular Emergencies: A Systematic Review

Caitlin S. Brown[1*], Lucas Oliveira J. e Silva[2], Alicia E. Mattson[1], Daniel Cabrera[2], Kyle Farrell[3], Danielle J. Gerberi[4] and Alejandro A. Rabinstein[5]

Nicardipine Versus Clevidipine

There were three observational studies [17–19] (total of 386 patients) comparing nicardipine and clevidipine, with mostly adult patients presenting with symptoms of nontraumatic brain hemorrhage. (Table 2) Their quality was overall suboptimal, with all estimates rated as having a high risk of bias. None of the included studies evaluated functional outcomes, and only one study [17] reported in-hospital mortality, showing fairly similar mortality rates between drugs (20% with nicardipine vs. 15.7% with clevidipine, RR 1.27, 95% CI 0.67 to 2.40).

As for BP-related outcomes, one study showed similar BP variability between nicardipine and clevidipine, as measured by the range of systolic BP measurements during infusion [19]. Time to reach goal BP was not statistically different in all three studies, but two of them had estimates pointing toward longer times with nicardipine as compared to clevidipine (mean differences ranging from +16 to +24) [17, 18]. The study by Rosenfeldt et al. [19], however, reported very similar times between groups (mean 65.5 with nicardipine vs. 65.8 min with clevidipine). Time within goal BP was also not significantly different between drugs in all three studies. Nevertheless, all estimates of mean or median differences pointed toward clevidipine having longer periods within goal BP. As for hypotension, two studies [18, 19] reported lower incidences of hypotension in nicardipine as compared to clevidipine, and one study [17] reported a higher incidence of hypotension with nicardipine. However, the estimated RRs had wide CIs with results not statistically significant likely due to limited sample sizes (i.e., important imprecision). Lastly, two studies reported very similar proportions of patients requiring rescue therapy with both drugs (RRs estimates of 0.94 and 1.10) [17, 18] (Table 4).

Brown CS, et al. Neurocrit Care. 2022 Oct;37(2):435-446.

Comparison of Intravenous Antihypertensives on Blood Pressure Control in Acute Neurovascular Emergencies: A Systematic Review

“In conclusion, the optimal IV antihypertensive for patients with acute neurologic emergencies remains unknown. The very low level of evidence quality for all outcomes across the three head-to-head comparisons in our systematic review highlights this knowledge gap and the need for more investigation. Future prospective randomized studies should ideally evaluate the most promising agents (nicardipine and clevidipine) and include information on BP variability (as an end point or as a therapeutic target) and functional outcomes.”

Brown CS, et al. Neurocrit Care. 2022 Oct;37(2):435-446.

Summary

- Per the AHA/ASA 2022 guideline update
  - Patients with a sICH presenting with SBP between 150 and 220 mmHg should have acute lowering of SBP to a target of 140 mmHg (range of 130 to 150 mmHg)
  - Blood pressure management should be initiated within the first hour of treatment
  - Continuous smooth and sustained control of BP should be achieved, avoiding peaks and large variability in SBP
- Based on current literature, data is insufficient to favor nicardipine or clevidipine

Learning Assessment Question

1. ZA is a 72 year old male presenting with confusions, nausea/vomiting, ataxia and GCS12. CT head shows ICH in cerebellar region. BP 195/95 mmHg, HR 58 bpm, and O2 sat 98% RA. What is the BP goal for this patient's blood pressure at this time?

A.Target of 140 mmHg with the goal of maintaining in the range of 130 to 150 mmHg
B. Target of < 130 mmHg
C. Permissive hypertension
D. Decrease MAP by 25% in first hour

Learning Assessment Question

Answer: a. Target of 140 mmHg with the goal of maintaining in the range of 130 to 150 mmHg

Explanation

In ZA's case, a 72-year-old male with cerebellar intracerebral hemorrhage (ICH), the appropriate blood pressure (BP) goal is to target a systolic BP of 140 mmHg, maintaining it within 130-150 mmHg. This strategy, based on American Heart Association/American Stroke Association guidelines, balances hematoma growth prevention and adequate brain perfusion. Options (b), (c), and (d) are incorrect as they either target overly aggressive BP reduction, allow permissive hypertension, or focus on mean arterial pressure (MAP) without considering specific systolic BP targets for optimal management.

Learning Assessment Question

2. ZA is a 72 year old male presenting with confusions, nausea/vomiting, ataxia and GCS12. CT head shows ICH in cerebellar region. BP 195/95 mmHg, HR 58 bpm, and O2 sat 98% RA. What is the best treatment option for blood pressure management at this time?

A. Nicardipine
B. Diltiazem
C. Labetalol
D. None of the above

Learning Assessment Question

Answer: a. Nicardipine

Explanation

Nicardipine is a preferred agent for blood pressure management in patients with ICH because it provides rapid, controlled, and reliable blood pressure reduction while maintaining stable heart rate. This is particularly important when managing hypertension in patients with ICH to prevent hematoma expansion and ensure adequate perfusion to the surrounding brain tissue. Options (b), (c), and (d) are not the best choices because they either have a less favorable hemodynamic profile or do not provide the appropriate level of blood pressure control needed in this clinical scenario.

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Blood Pressure Management in ICH

Gabrielle Procopio, PharmD, BCPS

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