

Assessment of Cerebral Perfusion Pressure (CPP) and Intracranial Pressure (ICP) in Patients with Acute Intracerebral Hemorrhage (ICH) Receiving Aggressive Blood Pressure Management with Clevidipine: An ACCELERATE Analysis

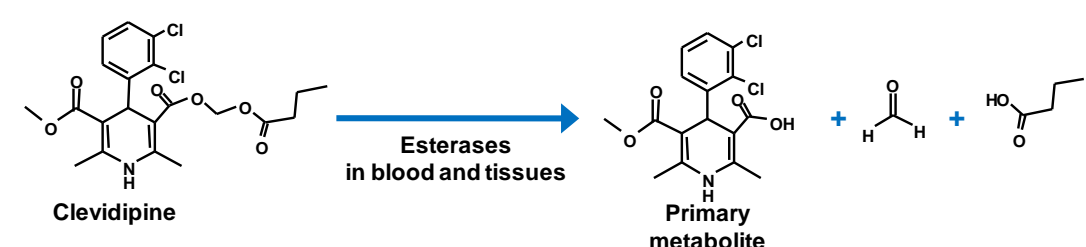
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Background

The ACCELERATE trial evaluated the safety and efficacy of intravenous (IV) clevidipine in patients with intracerebral hemorrhage (ICH) receiving aggressive blood pressure (BP) management

- Clevidipine is a rapidly-acting IV antihypertensive agent and an arterial- and vascular-selective dihydropyridine calcium channel blocker^{1,2}
 - approved by the U.S. FDA in 2008 for the reduction of BP when oral therapy is not feasible or not desirable¹
 - lipid-soluble agent that reduces BP by decreasing systemic vascular resistance^{1,2}
 - metabolized through rapid hydrolysis by esterases in the blood and extravascular tissues; unlikely to be affected by hepatic or renal dysfunction^{1,2}
 - pharmacokinetic half-life of ~1 minute^{1,2}



- In the U.S., ICH occurs in about 50,000 to 60,000 patients per year^{3,4}
 - high mortality (50% at 1 year) and limited recovery (only 20% of patients have independence at 6 months)⁴
 - hematoma growth is associated with poor outcome⁴; 72% of ICH patients show some hematoma growth in the first 24 hours,⁵ and 38% have significant (>33%) growth⁴
 - BP control in ICH patients with BP elevation may reduce hematoma growth^{4,6,7}
 - Rapid and aggressive BP management in acute stroke may reduce hemorrhagic risk, but raises potential concerns about intracranial pressure (ICP) and maintenance of cerebral perfusion pressure (CPP)
 - AHA guidelines⁴ for ICH management recommend monitoring ICP in patients with clinical deterioration or suspected elevated ICP while reducing systemic hypertension to maintain CPP >60 mmHg

- The open-label, single-arm ACCELERATE trial investigated aggressive BP management with IV clevidipine in this clinical setting

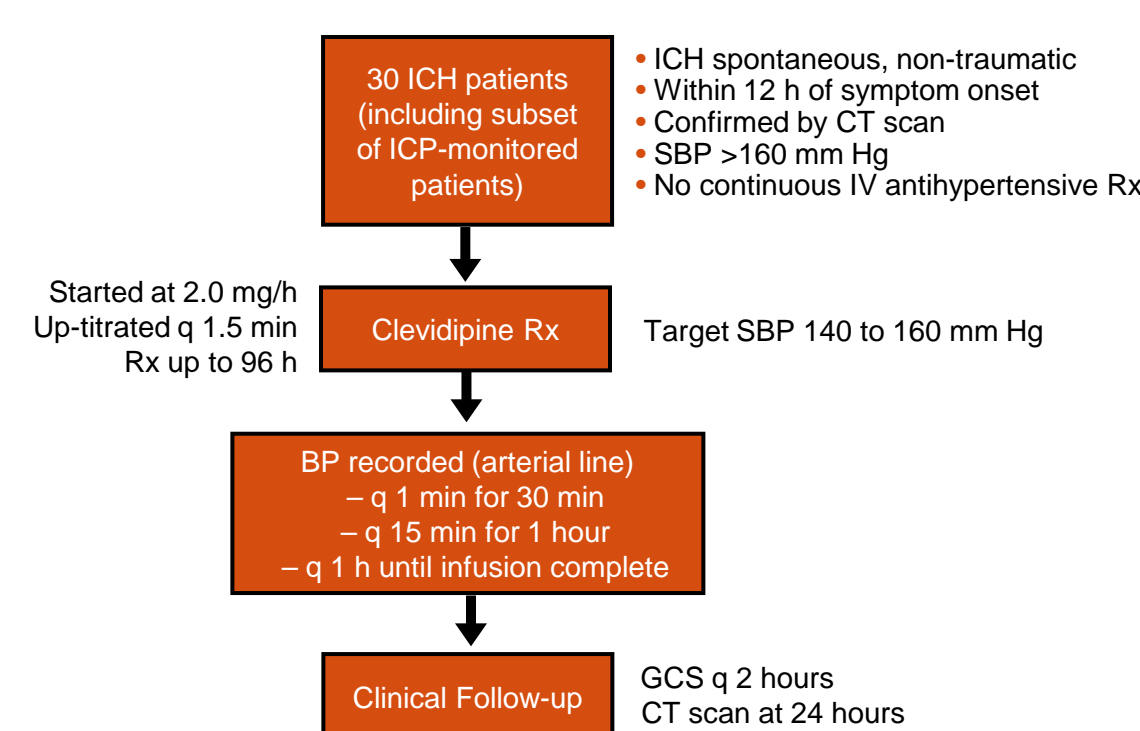
ACCELERATE Investigators

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Methods

ACCELERATE study design: Prospective, open-label, single-arm, multicenter trial in the U.S. and Germany

Figure 1. ACCELERATE Trial



Primary endpoint: Time to achieve target systolic BP (SBP)

Inclusion criteria included: Patients ≥18 years presenting with spontaneous (non-coagulopathic), non-traumatic ICH within 12 hours of symptom onset; ICH confirmed by computed tomography (CT); SBP >160 mm Hg measured by arterial line at baseline (immediately prior to clevidipine initiation)

Exclusion criteria included:

- Continuous IV antihypertensive treatment prior to clevidipine (bolus labetalol or hydralazine allowed)
- ICH related to trauma; aneurysmal subarachnoid hemorrhage; aortic dissection; or acute myocardial infarction on presentation
- Glasgow coma score (GCS) <5 and fixed/dilated pupils
- Intolerance or allergy to calcium channel antagonists, soybean oil or lecithin; or known liver failure, cirrhosis or pancreatitis

Clevidipine dosing: Initially 2.0 mg/h for 1.5 minutes; titrated by doubling infusion rate up to every 1.5 minutes to target SBP or to a maximum infusion rate of 32 mg/h

Treatment goal: Reduce SBP to ≤160 mm Hg, ≥140 mm Hg

Assessments (all patients) included:

- Intra-arterial BP monitoring, recording BP every minute during first 30 minutes of treatment
- Baseline and post-baseline GCS, NIHSS
- Baseline and 24-hour non-contrast brain CT scans and measurement of ICH volume
- CT scan assessments performed by two physician readers blinded to patient identity and time point of scan (baseline or 24 hours)
- ICH volume measured by ABC/2 method

ICP monitoring (subset of ICP patients):

- Eligible patients received ICP monitoring
- To be eligible for the ICP substudy, patients had to have approximately 3 hours of ICP monitoring while receiving clevidipine
- ICP measured every 30 min for the first 3 hours, then every hour until clevidipine infusion stopped; just prior to each clevidipine dose adjustment, and every 5 min for 15 min afterward; and every 10 min if ICP above 20 mm Hg, until it had fallen below 20 mm Hg

Results

Study Population

- 35 patients with acute, non-traumatic ICH were enrolled and treated with clevidipine
- Among this population, 7 patients were enrolled who required ICP monitoring for ≥3 hours while receiving clevidipine
- 1 patient who had prior treatment with IV mannitol was excluded from analysis
- We present preliminary study data from:
 - Analysis of patients with evaluable CT scans (n=30); and
 - A separate analysis of CPP and ICP in ICP-monitored patients (n=6)
- Calculations / definitions: CPP = MAP – ICP; MAP = (1/3 x SBP) + (2/3 x DBP)

Table 1. Demographics and Baseline Characteristics (Patients with Evaluable CT Scans, n=30)

Parameter	n (%)
Male	26 (86.7)
Age, years	Mean (SD) 62 (11.5) Median (Q1, Q3) 64 (55.0, 73.0)
Race	n (%)
Asian	3 (10.0)
African American	8 (26.7)
White	19 (63.3)
Medical history	
Hypertension	29 (96.7)
Coronary artery disease	3 (10.0)
Heart failure	0 (0.0)
Diabetes	2 (6.7)
ICH	1 (3.3)
Ischemic stroke	1 (3.3)
Systolic blood pressure	Mean (SD) 187 (21.1) Median (Q1, Q3) 183 (168.0, 195.0)
Diastolic blood pressure	87 (12.7) 86 (79.0, 94.0)
Glasgow Coma Score (GCS)	13 (3.3) 14 (13.0, 15.0)
NIH Stroke Scale Score (NIHSS)	13 (8.8) 11 (6.0, 16.0)
Hematoma volume,* mL	25 (29.6) 15 (5.0, 29.0)
Symptom onset to start of therapy, hours	5 (2.0) 5 (4.0, 5.8)

*Based on recorded investigator assessment, not blinded central reading. Q1=1st quartile. Q3=3rd quartile.

Table 2. Hematoma Locations (n=30)

Location	Patients n (%)
Right frontal	1 (3.3)
Right parietal	1 (3.3)
Right occipital	1 (3.3)
Right deep gray (Basal ganglia, thalamus)	15 (50.0)
Left frontal	1 (3.3)
Left occipital	1 (3.3)
Left deep gray (Basal ganglia, thalamus)	7 (23.3)
Pons	2 (6.7)
Midbrain	1 (3.3)

Safety/Tolerability: The adverse events observed in this study were consistent with prescribing information for clevidipine and expected events in hemorrhagic stroke.

Figure 4. Hematoma Volume at Baseline and 24 Hours (n=30)

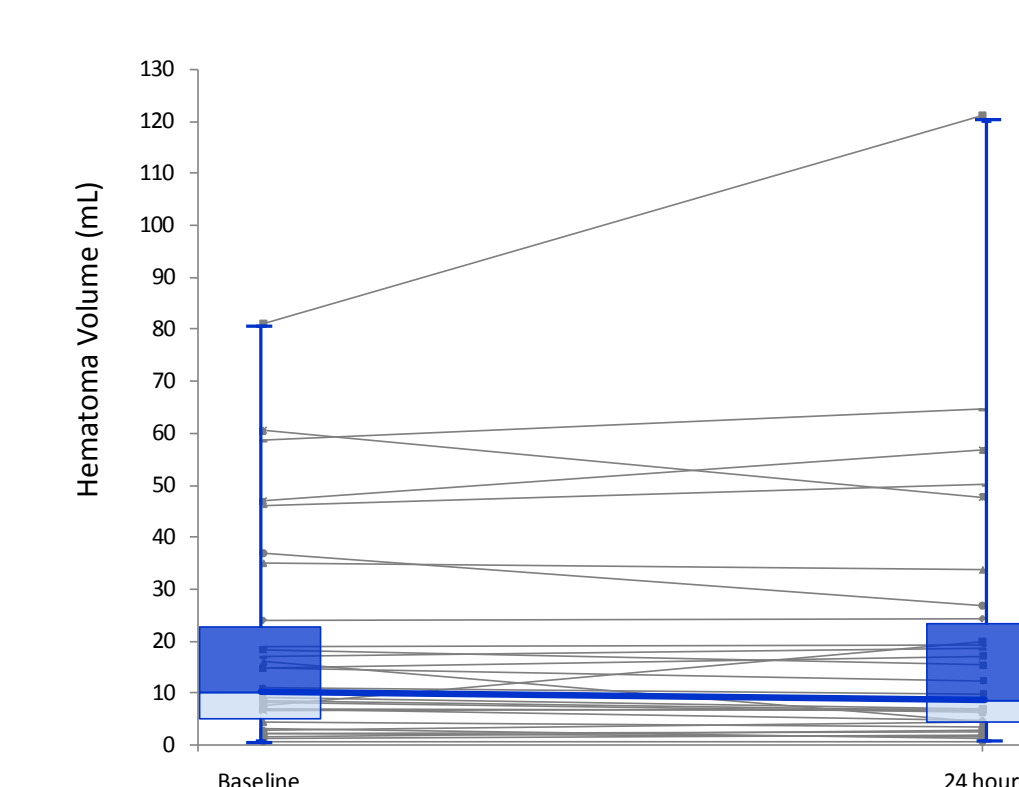


Figure 2. Mean Change in Systolic Blood Pressure with Clevidipine (Patients with Evaluable CT Scans, n=30)

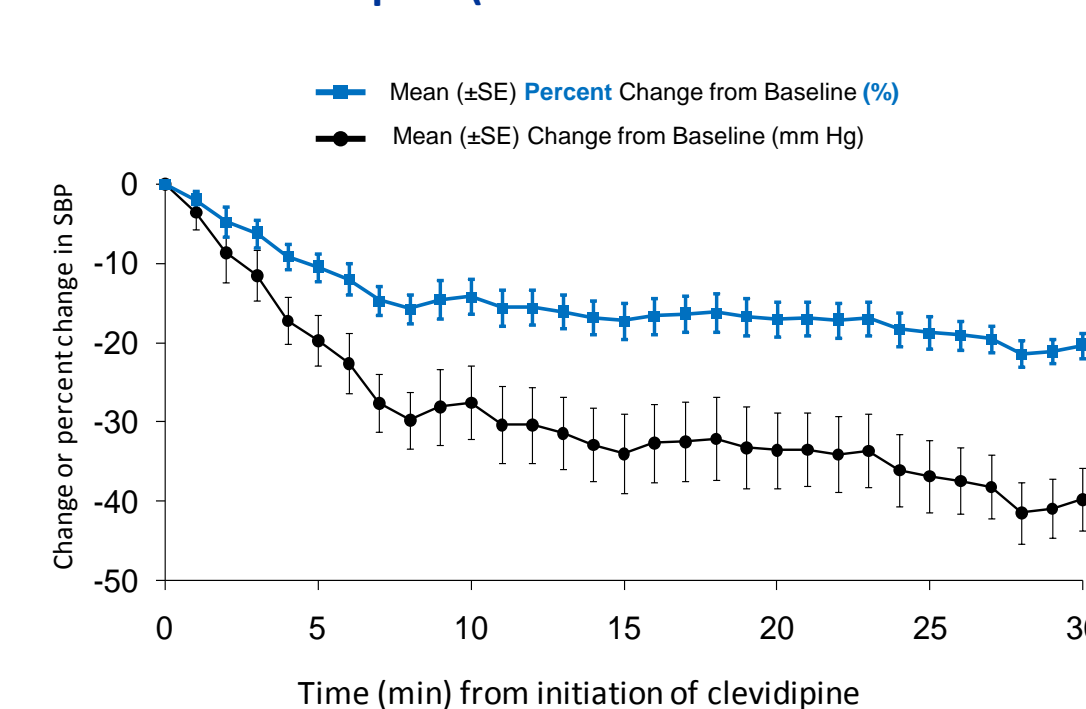


Table 3. Hematoma Volume (mL)

Patient Group	Median*			
	Baseline	24 hours	Change	% Change
All patients with evaluable CT scans (n=30)	9.9	8.4	-0.2	-3.5
Time of <5 hours from symptom onset to infusion start (n=15)	8.4	6.5	-1.0	-9.0
Time of ≥5 hours from symptom onset to infusion start (n=15)	14.6	15.4	0.5	8.4
Baseline SBP of ≤180 mm Hg (n=13)	8.9	9.9	0.6	10.4
Baseline SBP of >180 mm Hg (n=17)	14.6	6.8	-0.9	-16.0
Baseline hematoma volume of <30 mL (n=23)	7.5	6.5	-0.3	-4.8
Baseline hematoma volume of ≥30 mL (n=7)	46.8	50.0	4.1	9.0
Age <65 years (n=17)	6.9	6.5	-0.4	-4.8
Age ≥65 years (n=13)	18.3	19.3	0.5	2.7

*Based on blinded central readings. Median values from total n in each comparison. SBP = systolic blood pressure. CT = computed tomography.

Figure 5. Mean SBP and Mean MAP by Time (ICP-monitored Patients)

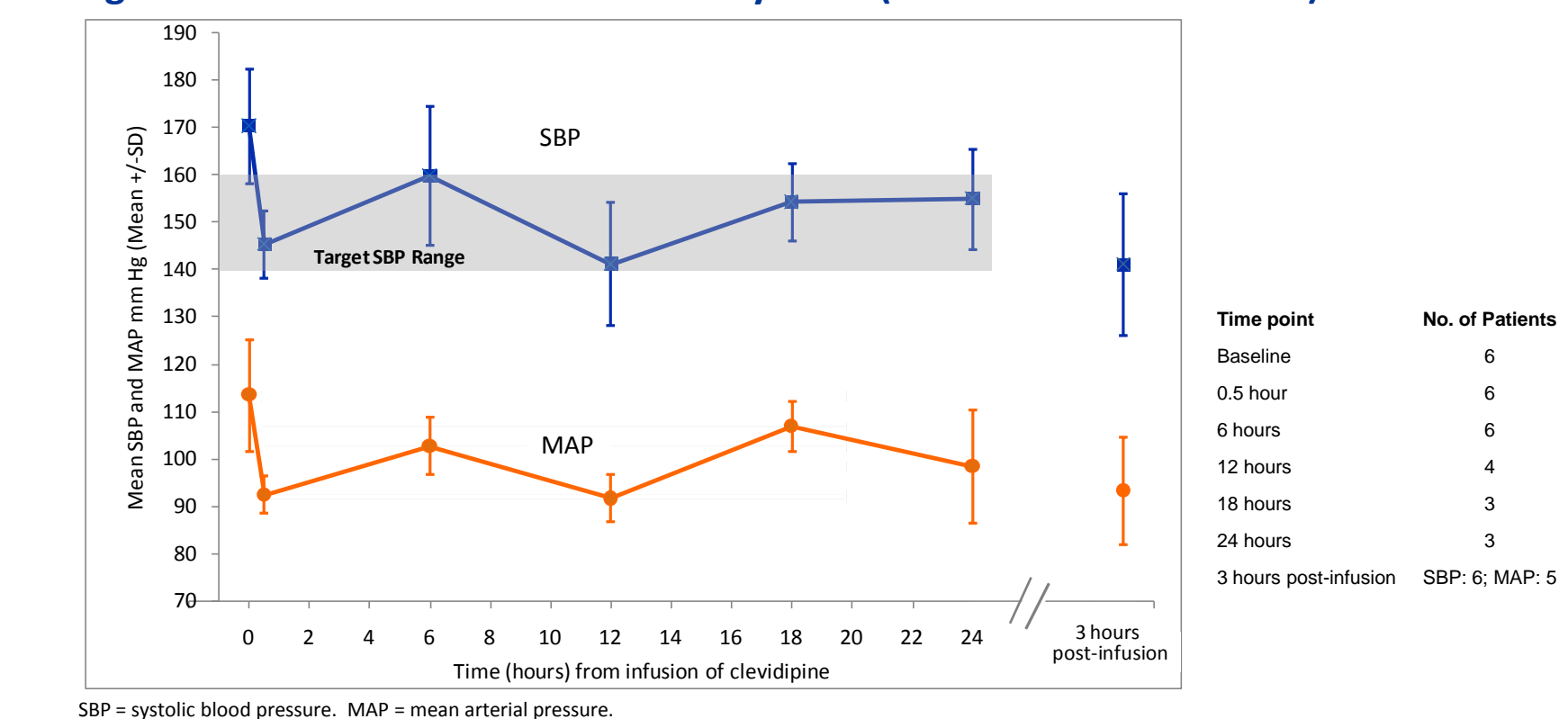
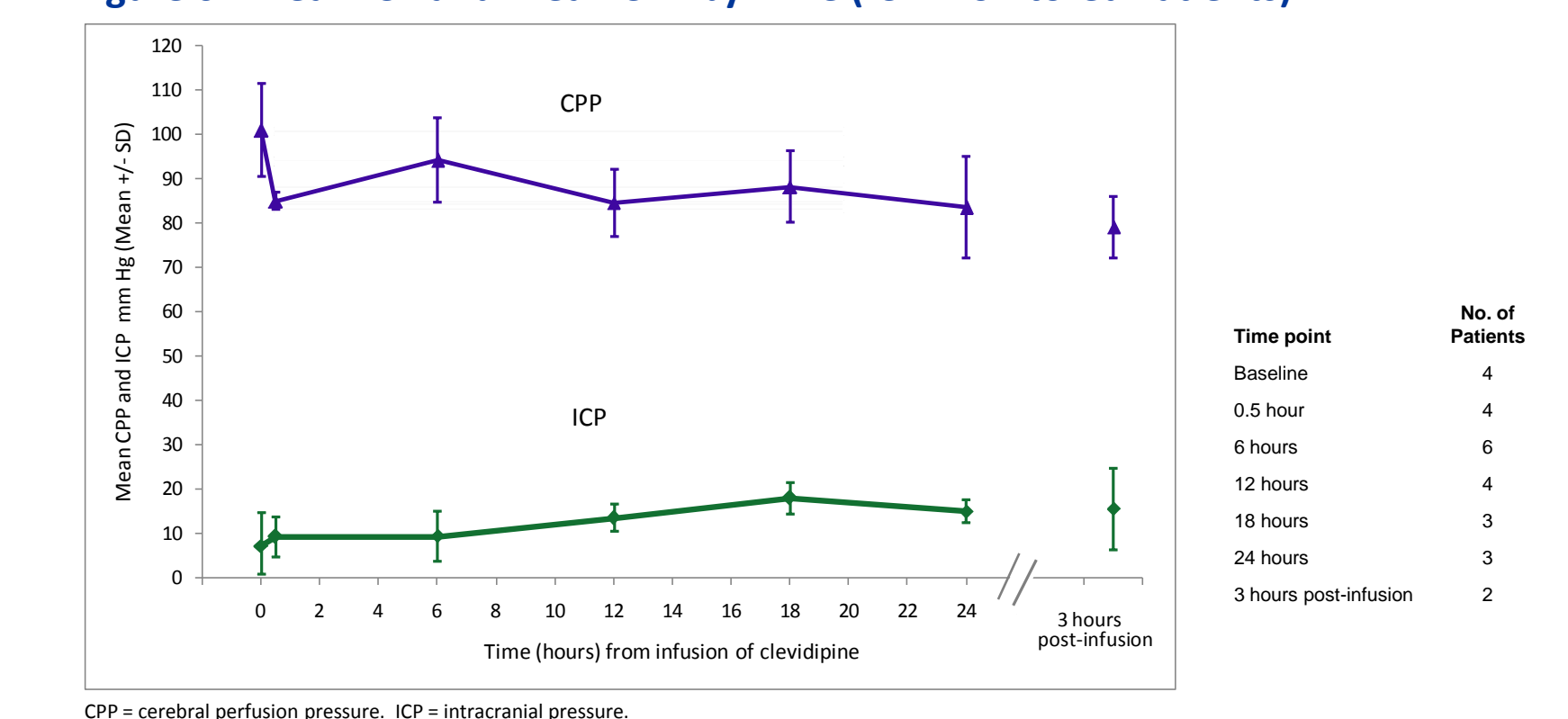


Figure 6. Mean ICP and Mean CPP by Time (ICP-monitored Patients)



Conclusions

- In ICH patients requiring ICP monitoring, CPP and ICP remained in desirable ranges during and after treatment with clevidipine to manage elevated SBP
- No meaningful increases or other clinically meaningful changes were observed in ICP
- Patients with acute ICH had minimal intracerebral hematoma volume change after SBP reduction with clevidipine
- The finding of minimal hematoma change did not vary among subgroups for age, baseline SBP, time to presentation or hematoma volume
- Safety profile with clevidipine in the 6 ICH patients requiring ICP monitoring was consistent with previous experience with clevidipine
- Clevidipine was well-tolerated and effective for managing BP in this study of critically ill patients
- Further studies of clevidipine in this setting are warranted

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Disclosures

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