
The ACCELERATE Study

**Evaluation of IV clevidipine in patients with
intracerebral hemorrhage and acute hypertension**

First report
(Interim analysis)

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Lynch, on behalf of the ACCELERATE Investigators

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Disclosures

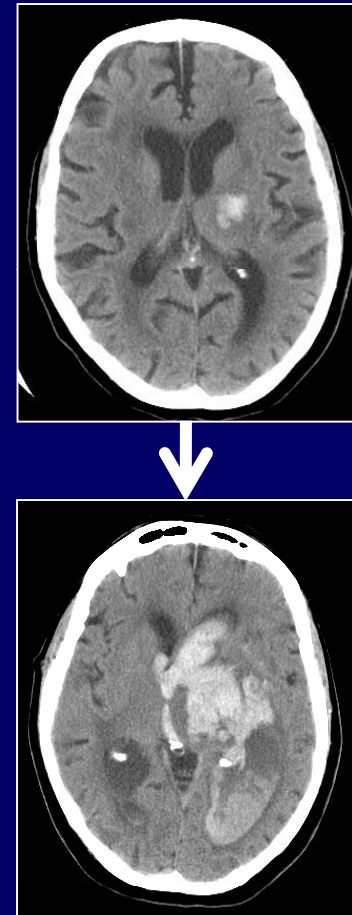
- **The Medicines Company**
 - Sponsor of the trial
 - Scientific consultant
- **EKR (and predecessors PDL, ESP Pharma)**
 - Prior speaker

Introduction

- **Intracerebral hemorrhage (ICH) causes 10-15% of all first-ever strokes**
- **Overall incidence is 10-20 per 100,000**
 - 40-50,000 patients present per year in the USA
 - 55 per 100,000 in African Americans and Japanese
- **30-day mortality is 35%-52%**

Hematoma expansion in ICH

- 73% of patients show some hematoma expansion over first 24 hours¹
- 38% have significant (>33%) expansion²
- 26% have expansion within 1 hour²
- 26% growth of hematoma volume in first 24 hours in the placebo group of the FAST trial³



BP and hematoma enlargement

- **Observed enlargement**

	Ohwaki et al.¹		Fujii et al.²	
Systolic BP, mm Hg	<140	<160	<150	>200
Hematoma enlargement	9%	30%	8%	22%

- **Studies observational, not interventional**

1. Ohwaki et al. Stroke. 2004;35:1364-1367. 2. Fujii et al. J Neurosurg. 1994;80:51-57.

INTERACT

Hematoma Volume	Standard Rx (N=172)	Intensive Rx (N=174)	Difference	P-value
Mean increase, %	36.3	13.7	22.6	0.04
Mean increase, mL	2.7	0.9	1.7	0.12
Substantial growth,* % of patients	23	15	8	0.05

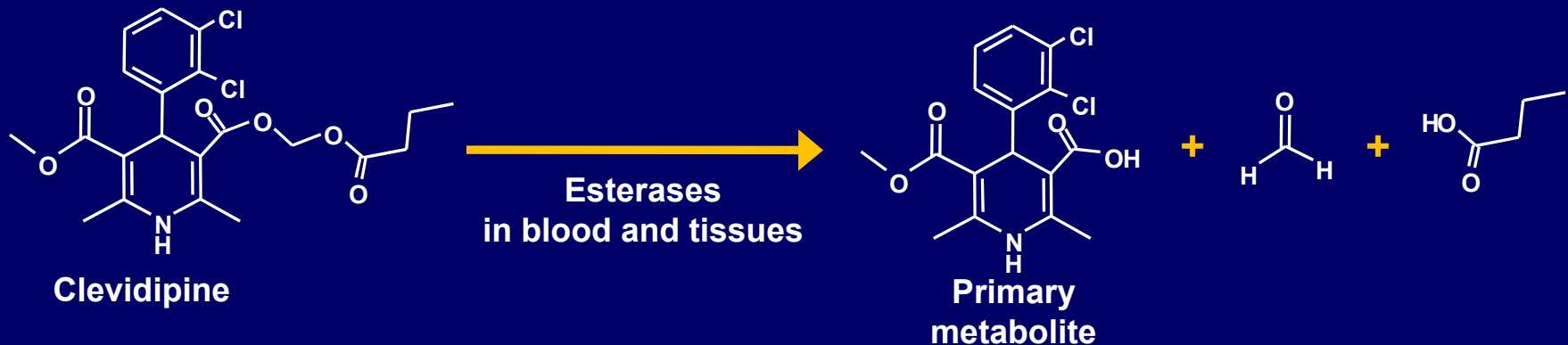
*>33% or 12.5 mL.

The ACCELERATE trial

- **Objective**
 - To evaluate the safety and efficacy of clevidipine for the management of blood pressure in patients with acute ICH and hypertension
- **Design**
 - Prospective, open-label, single-arm, multicenter trial
- **Centers**
 - 16 clinical centers in the US and Germany

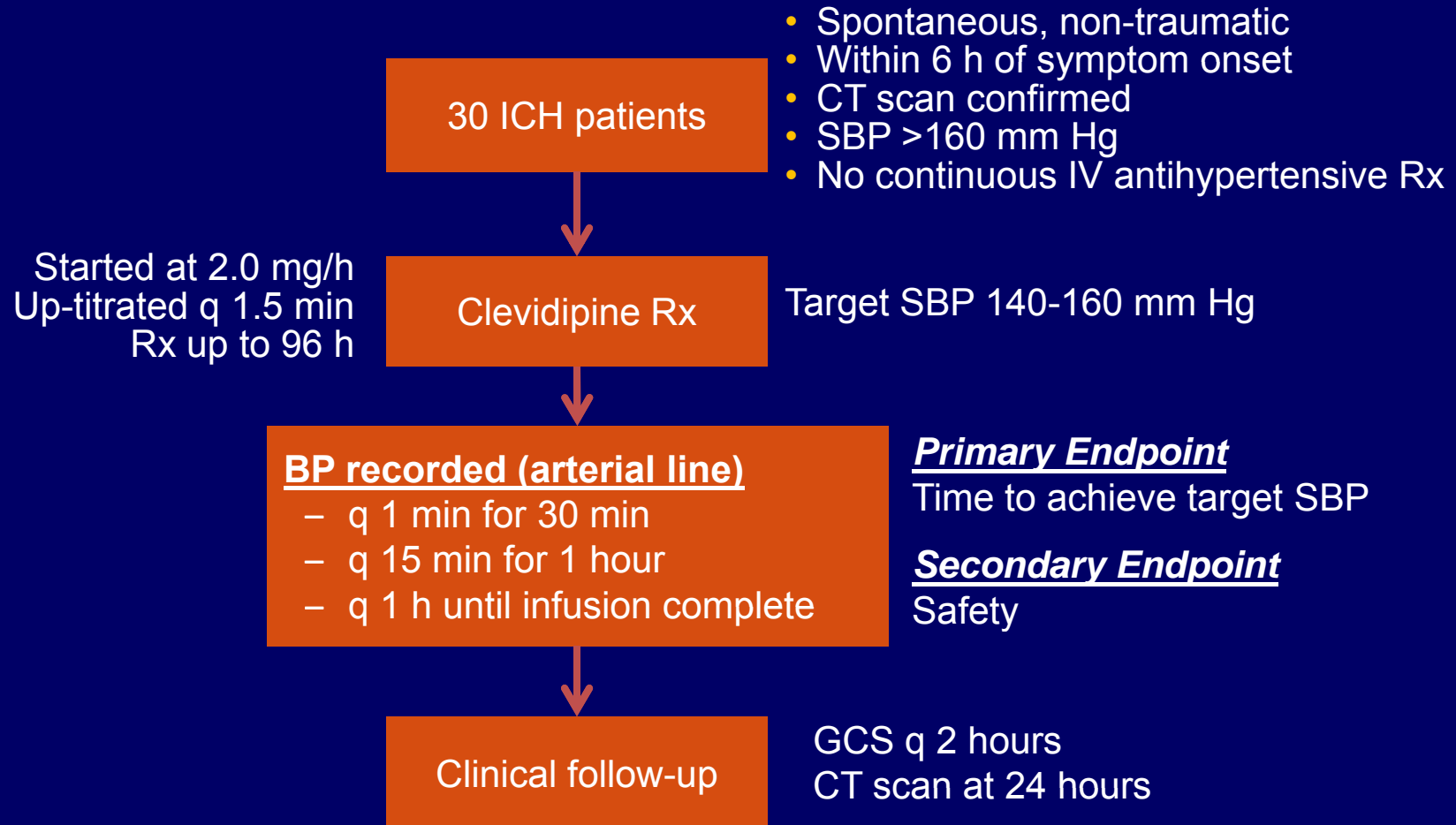
Clevidipine

- Rapidly acting, lipid-soluble, vascular-selective, L-type calcium channel blocker
- Effective half-life ~1 minute



Reproduced from Ericsson H, et al. Eur J Clin Pharmacol. 1999;55:61-67.

Study design



Exclusion criteria

- **Prior treatment with IV antihypertensive infusion (bolus labetalol or hydralazine permitted)**
 - **ICH related to trauma**
 - **Aneurysmal subarachnoid hemorrhage**
 - **Glasgow coma score (GCS) <5 and fixed/dilated pupils**
 - **Acute myocardial infarction on presentation**
 - **Intolerance or allergy to calcium channel antagonists, soybean oil or lecithin**
 - **Known liver failure, cirrhosis or pancreatitis**
-

Methods

- **Baseline measures**
 - Demographics, clinical exam including BP, GCS, NIHSS and CT measurement of ICH volume obtained
- **All patients had intra-arterial BP monitoring**
- **24 hours**
 - GCS, repeat non-contrast brain CT for measurement of ICH volume
- **ICH volume measured by ABC/2 method¹⁻³**

Patient characteristics (N=30)

Characteristic		n (%)
Gender	Male	24 (80)
Age, years	[Mean (SD)]	63.7 (11.2)
Race	Asian	2 (7)
	African American	10 (33)
	White	18 (60)
Medical history	Hypertension	29 (97)
	Coronary artery disease	4 (13)
	Heart failure	1
	Diabetes	3 (10)
	ICH	1
	Ischemic stroke	1

Clinical presentation at baseline

Baseline blood pressure, mm Hg

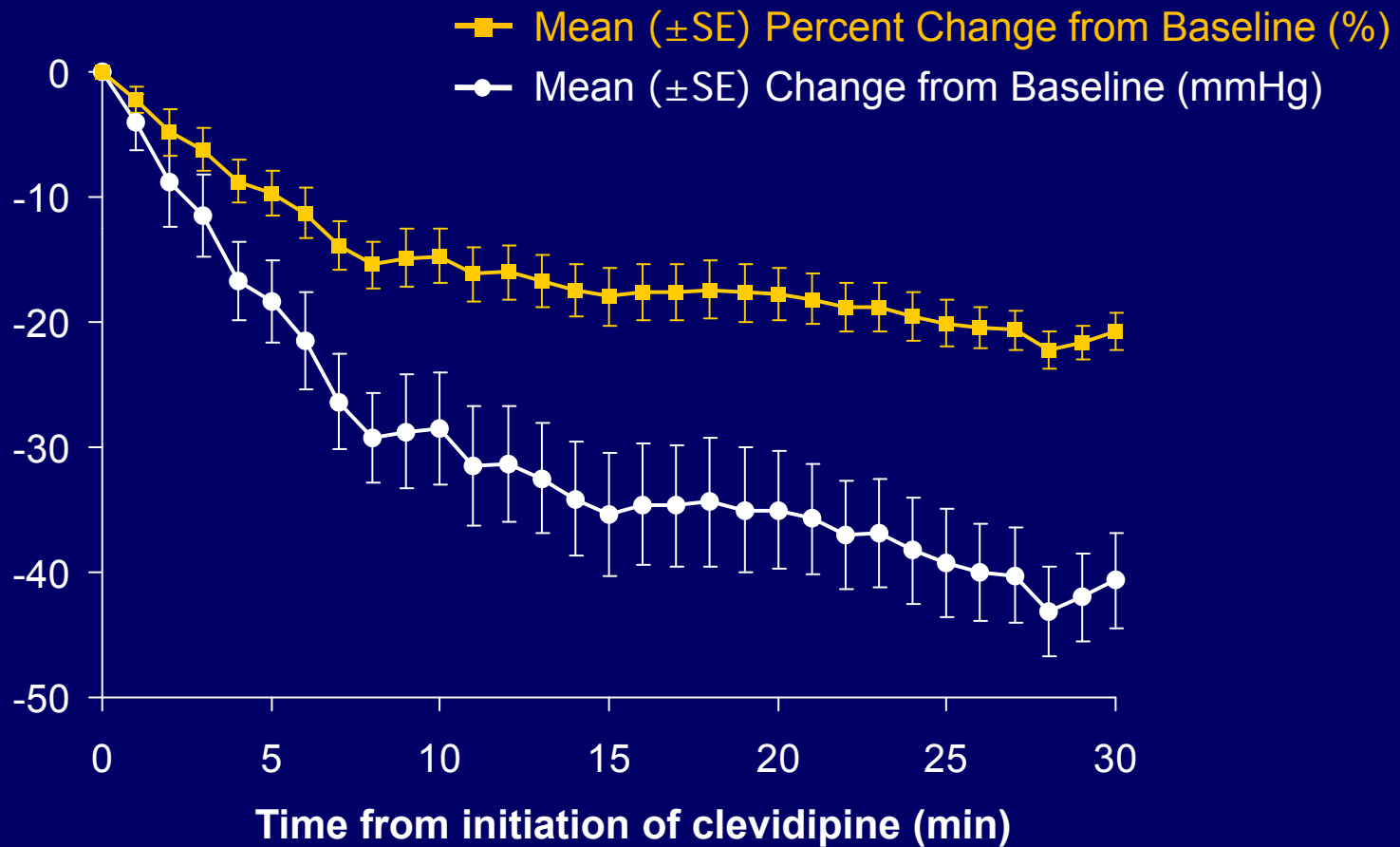
	Systolic	Mean (SD)	188	(20)
	Diastolic	Mean (SD)	85	(14)
Glasgow coma score		Mean (SD)	13	(3)
		Median (Q1, Q3)	14	(12, 15)
NIH stroke scale score		Mean (SD)	12	(8)
		Median (Q1, Q3)	11	(6, 17)
Hematoma volume,* mL		Mean (SD)	25.1	(30.1)
		Median (Q1, Q3)	13.5	(5, 31)
Symptom onset to start of therapy, h		Mean (SD)	4.7	(1.4)
		Median (Q1, Q3)	4.6	(3.9, 5.8)

*Based on Investigator assessment (N=30).

Results: BP control

Max. infusion rate to achieve target BP, mg/h	Mean (SD)	11.5	(11.6)
Time to target SBP (≤ 160 to ≥ 140 mm Hg), min	Median (95% CI)	6.5	(3, 10)
Patients at SBP ≤ 160 mm Hg within 30 min infusion start, n (%)	All treatment	30	(100%)
	As monotherapy	29	(97%)
Average infusion rate, mg/h	Mean (SD)	7.5	(5.2)
Infusion duration, h	Mean (SD)	30	(26)

Change in SBP



Results: Safety and tolerability

- **In the first 30 minutes (initial BP control)**
 - No patients with SBP <90 mm Hg
 - No pressors necessary
 - No observed hypotension
 - **Over remainder of treatment period, 3 patients developed hypotension**
 - 1 patient with SBP <90 mm Hg
 - All 3 patients promptly responded to stopping or decreasing clevidipine
 - **1 patient with normal baseline triglycerides had a level >300 mg/dL on infusion; resolved 6 hours post infusion**
 - **1 patient died (withdrawal of life support, GCS 6)**
 - **The most common (>10%) adverse events were pyrexia (n=6) and headache (n=5)**
-

Acute ICH studies: Baseline characteristics

	ACCELERATE N=30	INTERACT ¹		FAST ²		
		Standard Rx N=201	Intensive Rx N=203	Control N=268	rFVIIa 20 mcg N=276	rFVIIa 80 mcg N=297
Age, years	63.7 (11)	62 (13)	63 (12)	65 (14)	65 (14)	65 (14)
SBP baseline, mm Hg	188.4 (20.06)	182 (19)	180 (18)	180 (28)	179 (30)	182 (32)
GCS _{T=0 hr} *	14 (12,15)	14 (12,15)	14 (13,15)	15 (6,15)	14 (6,15)	14 (6,15)
NIHSS _{T=0 h}	10.5 (6,17)* 11.9 (8)	9 (5,16)*	9 (5,14)*	13 (6)	13 (7)	13 (7)
Hematoma volume _{T=0 hr} , mL	25.1 (30) [#]	12.7 (12)	14.2 (15)	22 (24)	24 (26)	23 (26)
Time from symptoms to therapy, h	4.6 (3.9, 5.8)*	4.7 (2.8, 7.3)*	4.0 (3.0, 5.3)*	2.67 (.63)	2.67 (.61)	2.67 (.61)

Data presented as mean (standard deviation) unless otherwise noted. *Median (range). [#]Based on Investigator assessment. rFVIIa = recombinant activated factor VII. 1. Anderson et al. Lancet Neurol. 2008;7:391-399. 2. Mayer et al. NEJM. 2008;358:2127-2137.

Acute ICH studies: BP control

	ACCELERATE N=30	INTERACT ¹		Liu-DeRyke et al ²	
		Standard Rx N=201	Intensive Rx N=203	Nicardipine N=34	Labetalol N=15
Target SBP, mm Hg	≥140 to ≤160	≤180	≤140	MAP <130	MAP <130
IV infusion of antihypertensive drugs	100%	27%	67%	100%	Bolus only
Baseline SBP, (mm Hg) [†]	188.4 (20.06)	182 (19)	180 (18)	185 (30)	191 (37)
SBP at 30 min, mm Hg [†]	148.6 (9.14)	173 [#]	162 [#]	NA	NA
SBP at 60 min, mm Hg [†]	152.4 (18.76)	167	153	NA	NA
% of patients achieving target BP within 1 h	100%	[100%*]	42%	33%	6%
% of patients achieving target BP within 6 h	100%	[100%*]	66%	NA	NA

* Target SBP for standard Rx in INTERACT trial was ≤180 mm Hg. [#]Estimated. [†]Mean (standard deviation). NA=not available.
1. Anderson et al. Lancet Neurol. 2008;7:391-399. 2. Liu-DeRyke et al. Neurocrit Care. 2008; 9:167-176.

Acute ICH studies: Hematoma volume

	ACCELERATE (Preliminary) [†] N=17	INTERACT ¹		FAST ²		
		Standard Rx N=172	Intensive Rx N=174	Control N=268	rFVIIa 20 mcg N=276	rFVIIa 80 mcg N=297
Hematoma volume _{T=0h} , mL	19.6 (21.8)	12.7 (12)	14.2 (15)	22 (24)	24 (26)	23 (26)
Hematoma volume _{T=24h} , mL	21.0 (31.7)	15.4 (14.7)	15.2 (17.5)	28 (31)	28 (30)	25 (28)
Absolute increase, [*] mL	1.4 (-5.1 to 8.0)	2.7 (1.4 to 4.0)	0.9 (-0.09 to 2.7)	7.5 (5.4 to 9.6)	4.9 (2.9 to 7.0)	3.7 (1.7 to 5.7)
Substantial growth, [^] n (%)	3 (18%)	40 (23%)	26 (15%) P= 0.05 [#]	NA	NA	NA

Data presented as mean ± standard deviation unless otherwise noted. *Mean (95% CI). [#]P value vs INTERACT standard Rx. [^] Increase in hematoma volume of >33% or >12.5 mL in first 24 hours. [†]Preliminary data, based on single (blinded) reader assessment of 17 patients with available data out of 30. rFVIIa = recombinant activated factor VII. 1. Anderson et al. Lancet Neurol. 2008;7:391-399. 2. Mayer et al. NEJM. 2008;358: 2127-2137.

Acute ICH studies: Proportional increase in hematoma volume

	ACCELERATE (Preliminary) [†] N=17	INTERACT ¹		FAST ²		
		Standard Rx N=172	Intensive Rx N=174	Control N=268	rFVIIa 20 mcg N=276	rFVIIa 80 mcg N=297
Proportional increase (%), mean (95%CI)	0.45 (-24.7 to 25.6)	36.3 (15.8 to 56.8)	13.7 (5.9 to 21.5) P =0.04 [#]	26 (20 to 32)	18 (13 to 24) P =0.09 [§]	11 (6 to 17) P <0.001 [§]

[†]Preliminary data, based on single (blinded) reader assessment of 17 patients with available data out of 30. [#]P value vs INTERACT standard Rx.

[§]P value vs FAST control group. rFVIIa = recombinant activated factor VII. 1. Anderson et al. Lancet Neurol. 2008;7:391-399; 2. Mayer et al. NEJM. 2008;358:2127-2137

ACCELERATE study limitations

- **Open-label, single arm study**
- **Modest sample size**
- **Short-term blood pressure endpoints**
- **Long-term functional outcomes not studied**

ACCELERATE study summary

- **In patients with acute, non-traumatic intracerebral hemorrhage administered clevidipine IV**
 - Target blood pressure reduction was achieved in 100% of patients within 30 minutes; 97% of patients with monotherapy
 - Median time to target was 6.5 minutes
- **There were no instances of hypotension and no need for pressors in the initial 30-minute period of BP control**
 - 3 patients subsequently developed hypotension. All 3 patients promptly responded to stopping or decreasing therapy

ACCELERATE study conclusions

- **Clevidipine is safe and effective for the management of blood pressure in non-traumatic ICH patients**
 - **Clevidipine achieves rapid, on-target BP control without overshoot during the treatment period**
 - **For initial BP control, additional agents are infrequently required**
 - **Rapid reduction in blood pressure has been associated with reduced hematoma expansion in other studies**
 - **Further studies of clevidipine are warranted**
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ACCELERATE study sites

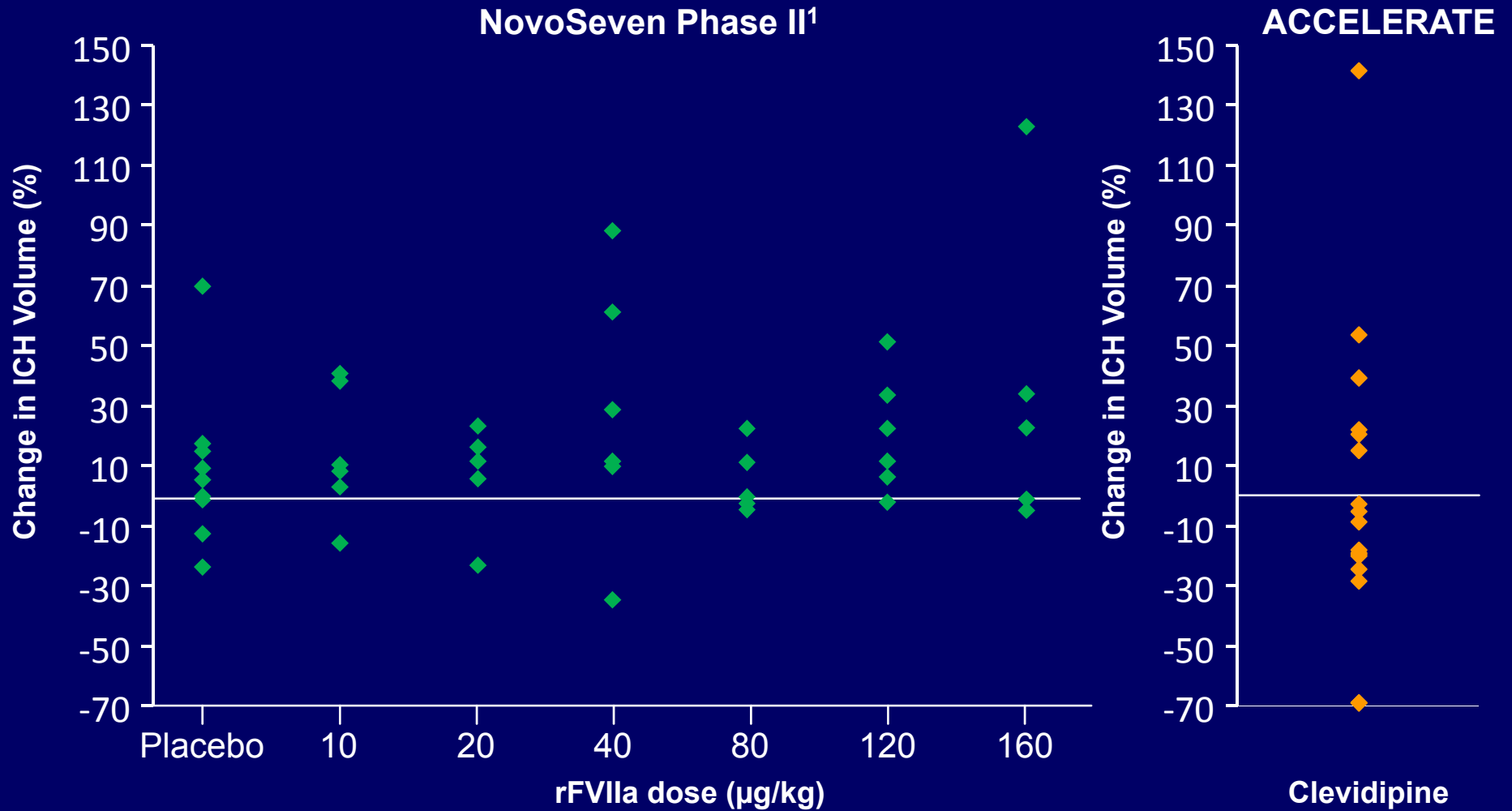
Investigator	Team	Institution
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Richard Riker	B Violette	Maine Medical Center
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Romergryko Geocadin	S Ledroux	The Johns Hopkins Hospital
Augusto Parra	A Leonard	University of Texas Health Science Center at San Antonio

Backup Slides

ACCELERATE: Changes in GCS and hematoma volume

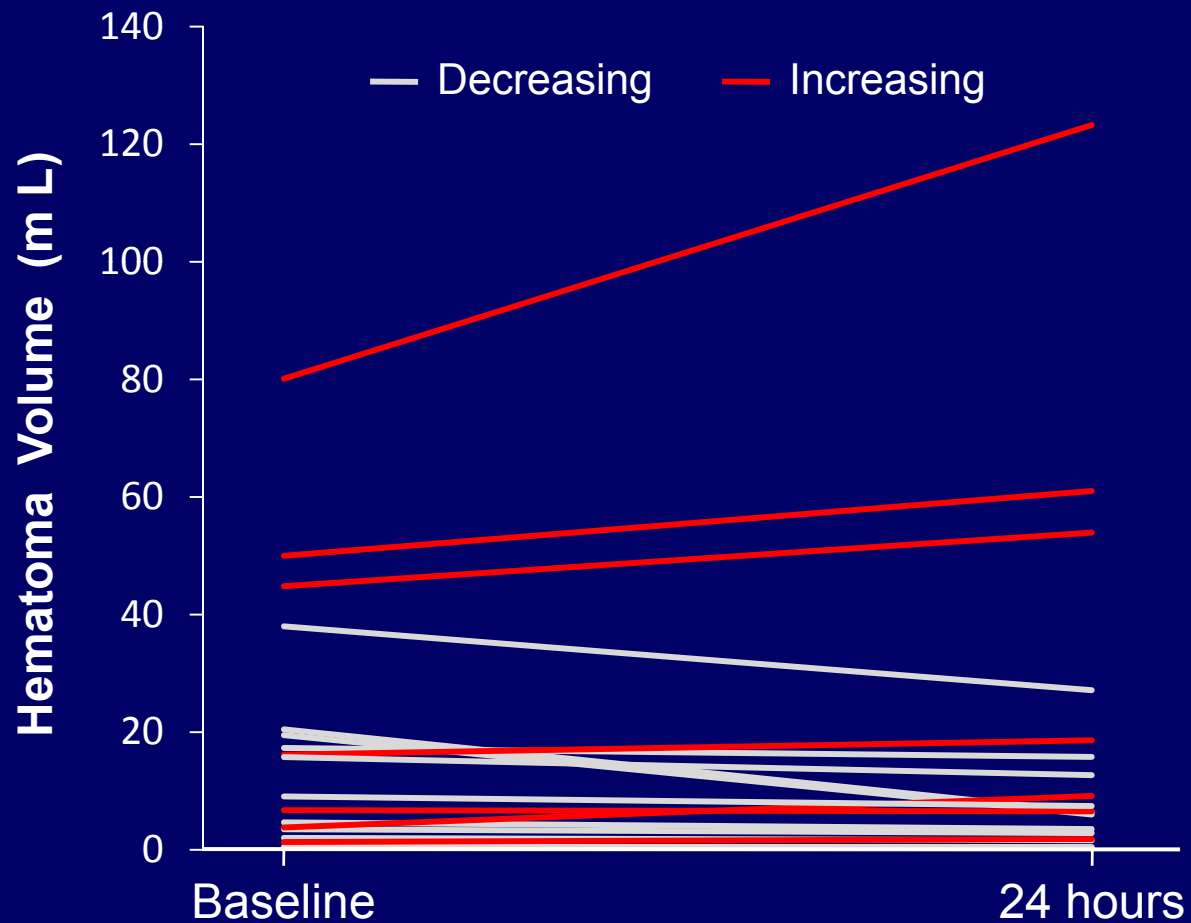
	Baseline Variable	24 Hours after Start of Infusion
GCS	n=21	n=21
Mean (SD)	13.2 (2.62)	12.3 (3.05)
Median (Q1, Q3)	15 (13, 15)	14 (10, 15)
Hematoma Volume (mL)	n=17	n=17
Mean (SD)	19.6 (21.8)	21.0 (31.7)
Median (min, max)	15.8 (0.5, 80.1)	7.4 (0.5, 123.3)

Change in ICH volume

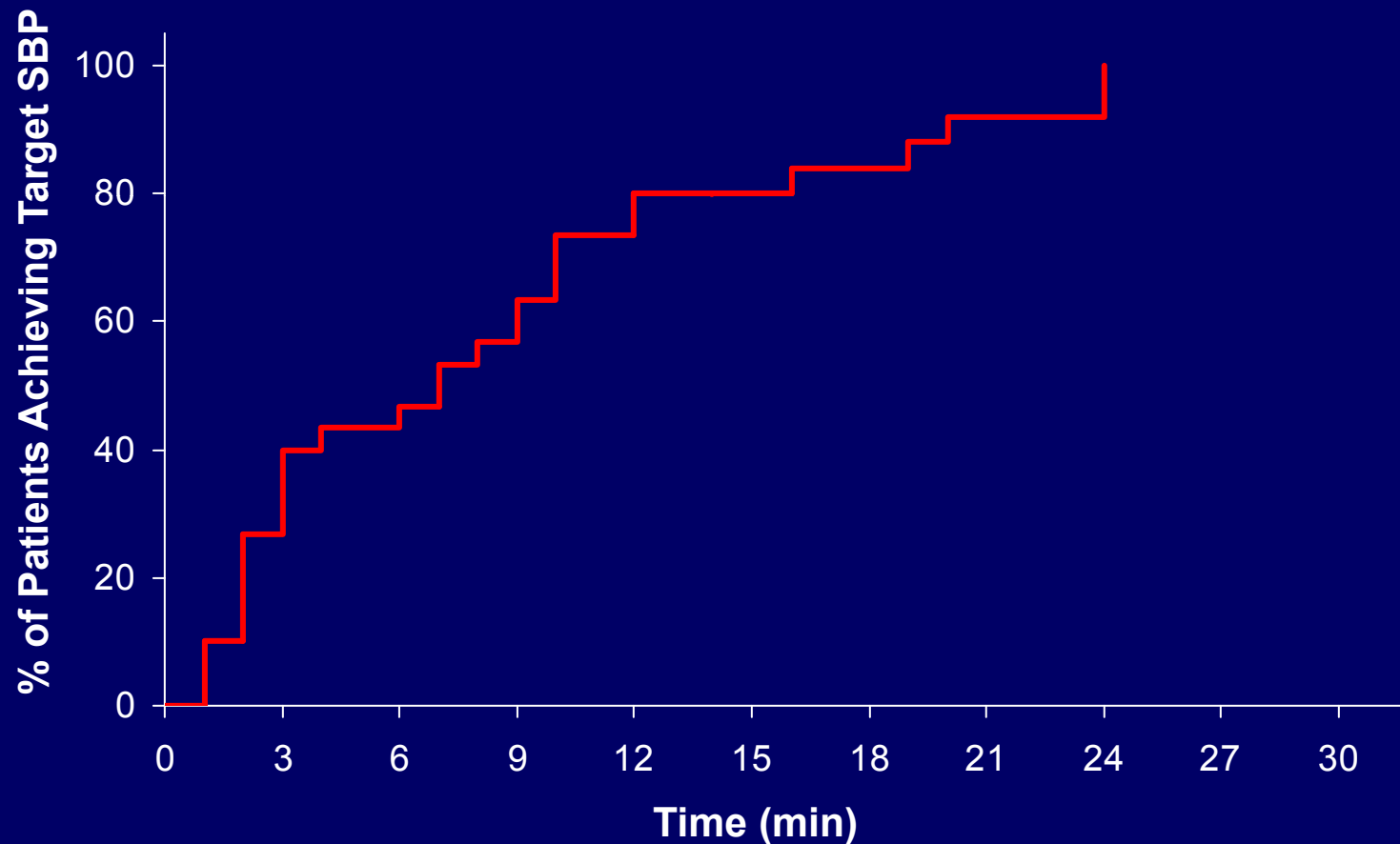


1. Mayer et al. Stroke. 2005; 36: 74-79.

ACCELERATE: ICH volume at baseline and 24 hours (N=17)

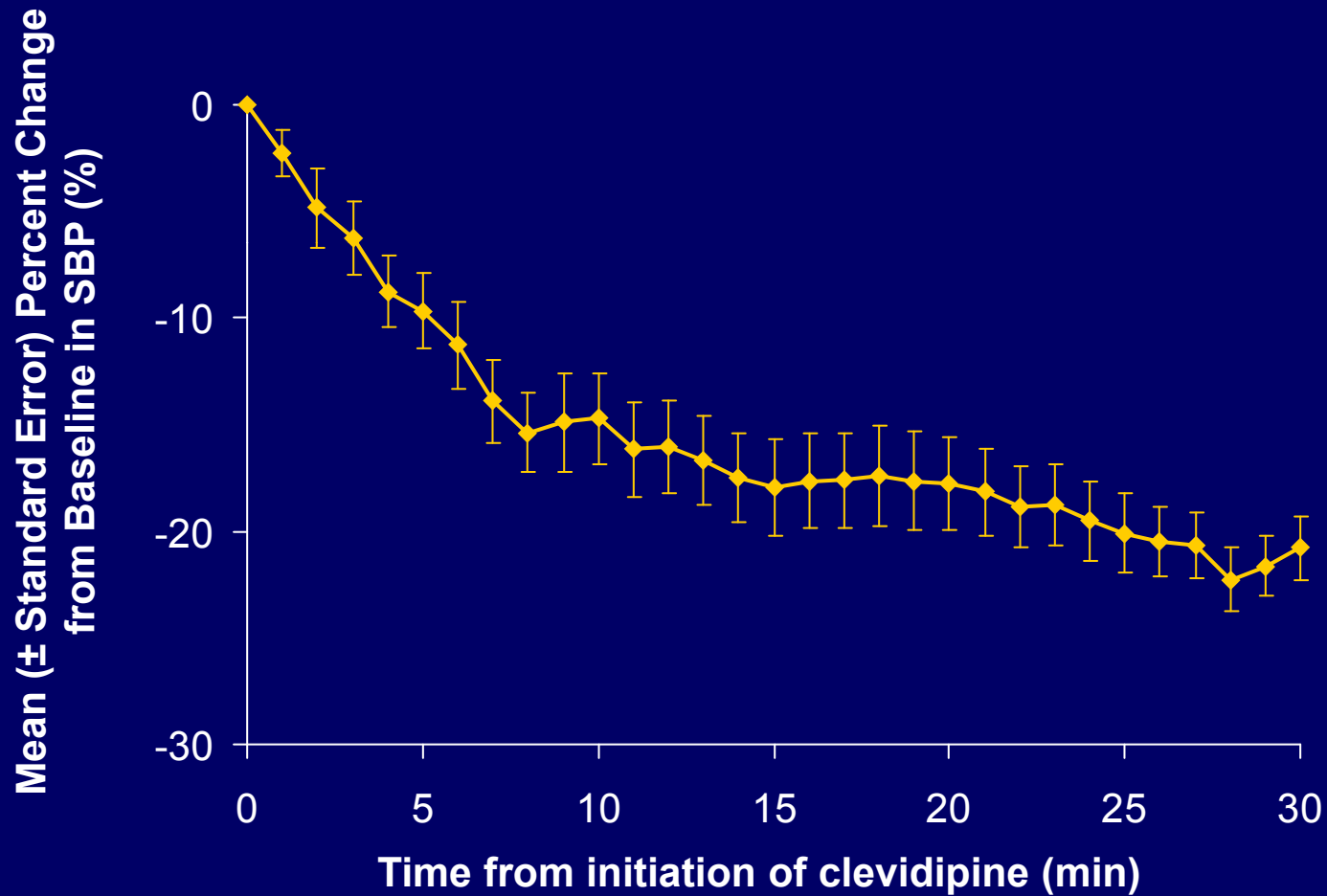


ACCELERATE: Time to target SBP

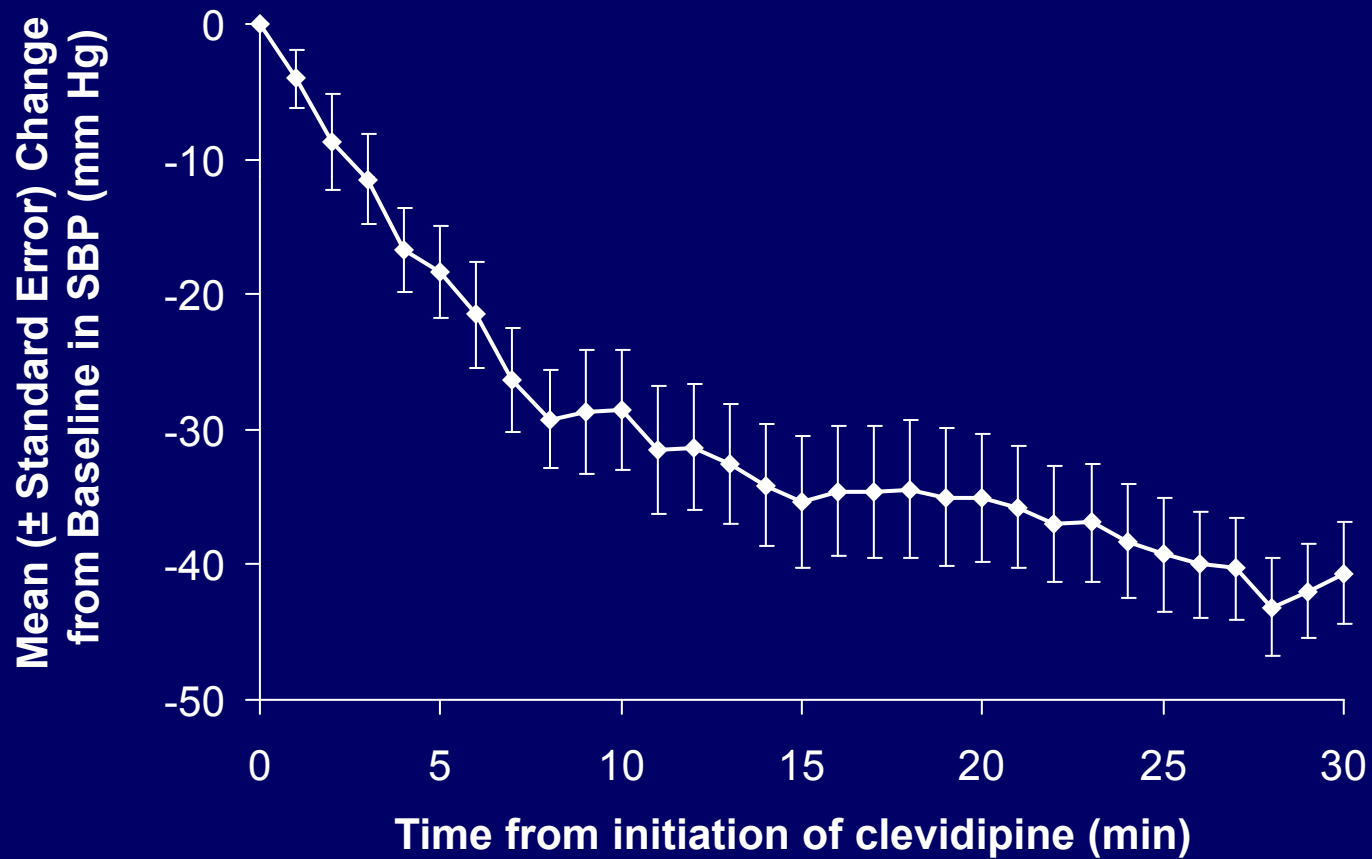


MITT population. SBP target range = 140 mm Hg \leq SBP \leq 160 mm Hg.

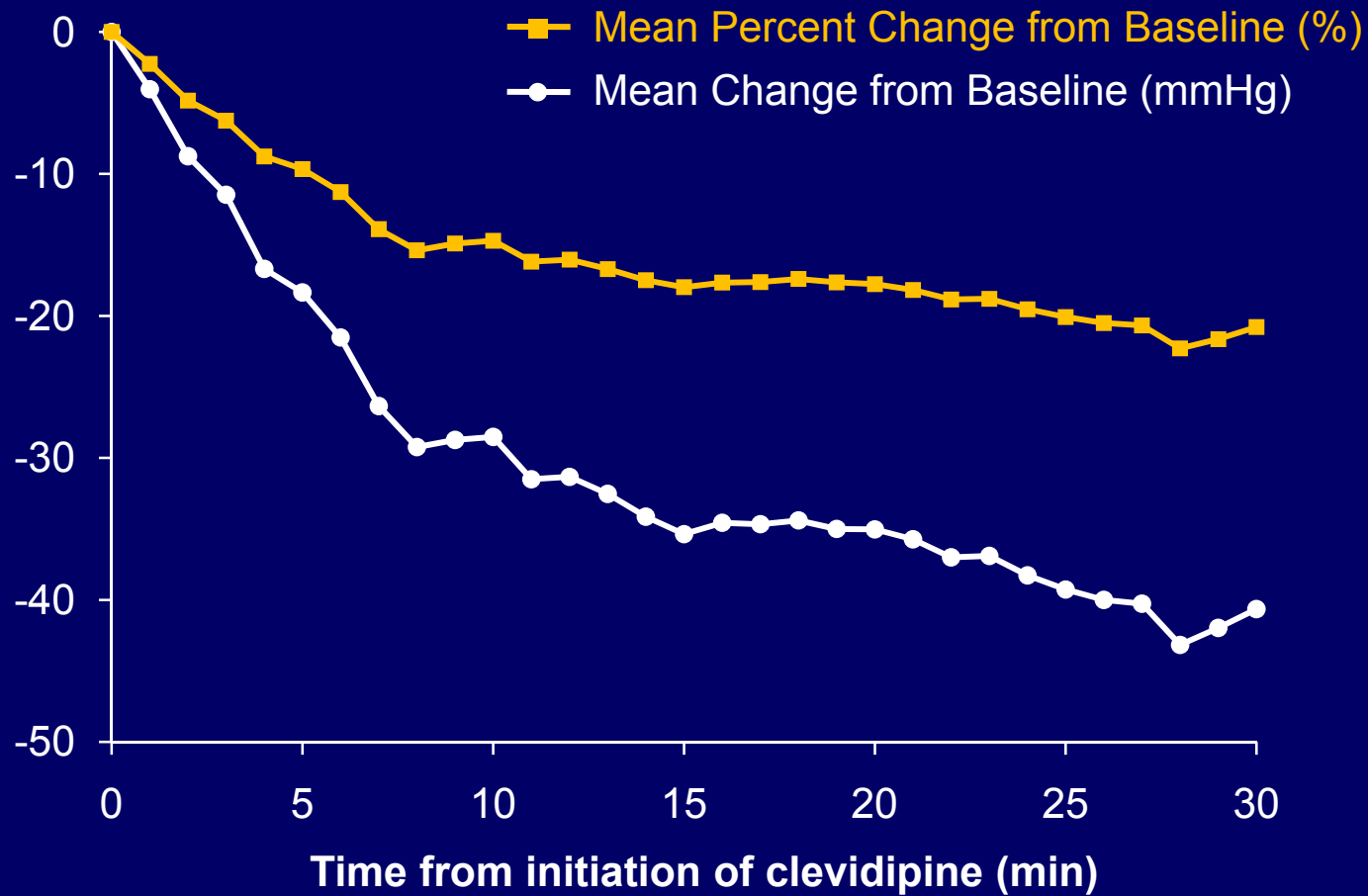
Mean percent change in SBP (%)



Mean change in SBP (mmHg)



Change in SBP



Inclusion criteria

Patients presenting with ICH:

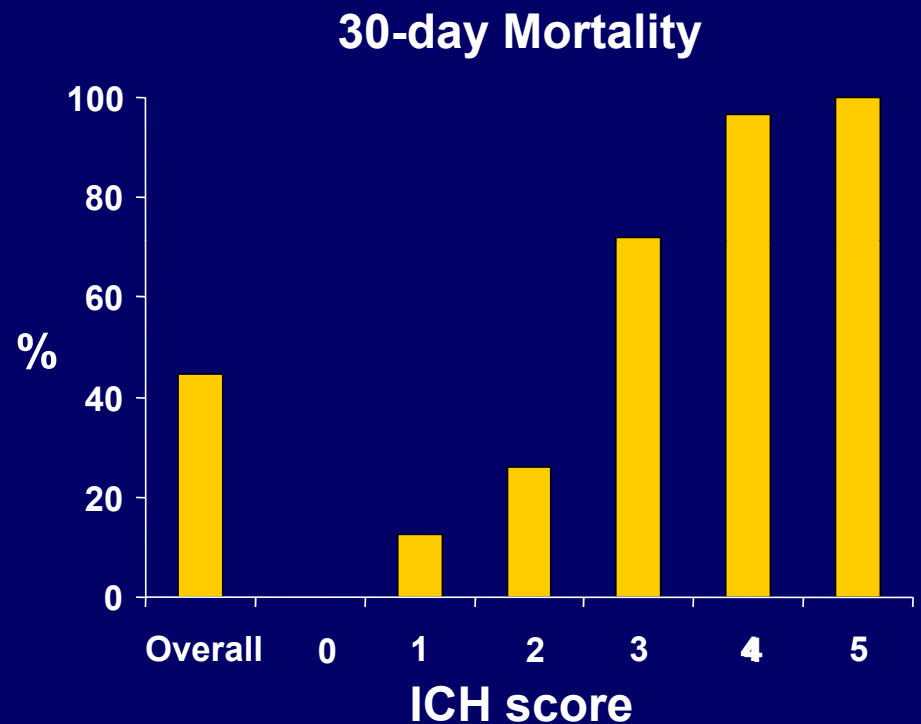
- **Spontaneous (non-coagulopathic)**
 - **Non-traumatic**
 - **Within 6 hours of symptom onset**
 - **Confirmed by CT**
 - **Systolic BP >160 mm Hg at baseline**
 - **Not on continuous IV antihypertensives**
-

Methods

- **Clevidipine dosing**
 - Started at 2.0 mg/h
 - Titrated by doubling infusion rate up to every 1.5 minutes up to target SBP or to a maximum infusion rate of 32 mg/h
- **Treatment goal**
 - Reduce SBP to ≤ 160 mm Hg, ≥ 140 mm Hg

Predictors of outcome: The ICH score

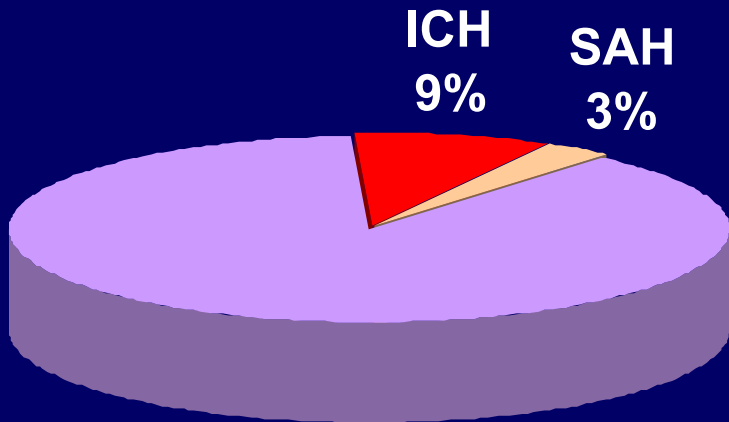
Component		ICH score points
GCS	3-4	2
	5-12	1
	13-15	0
ICH volume, cc	≥30	1
	<30	0
Intraventricular hemorrhage	Yes	1
	No	0
Infratentorial origin	Yes	1
	No	0
Age, years	≥80	1
	<80	0
Total ICH score		0-6



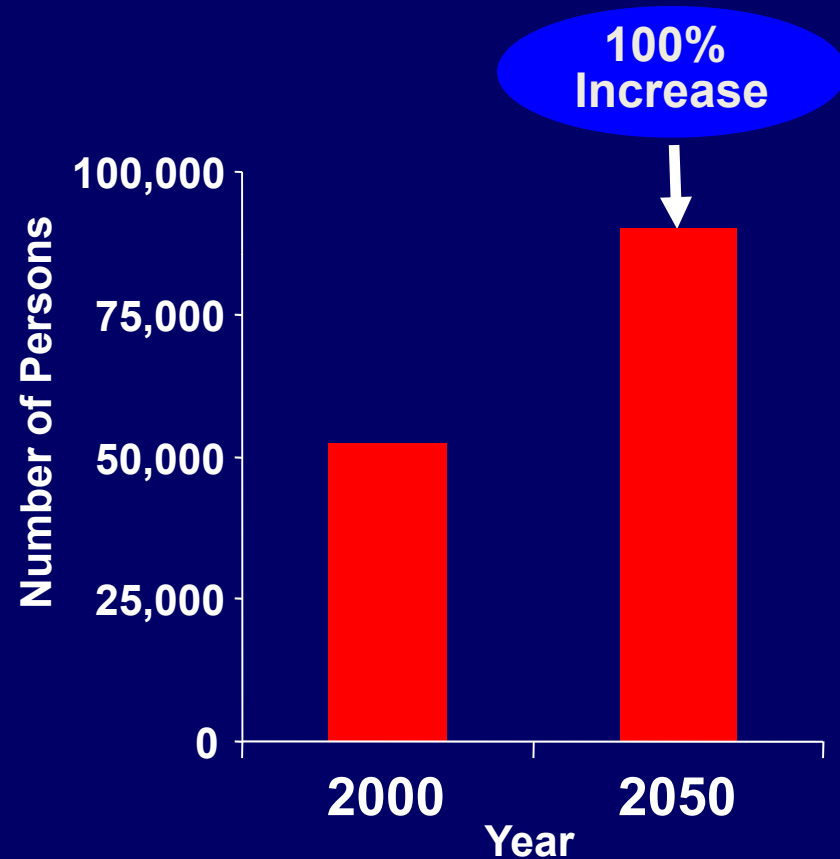
ICH is more common than SAH

Incidence predicted to increase

ICH Proportion of Strokes (US)

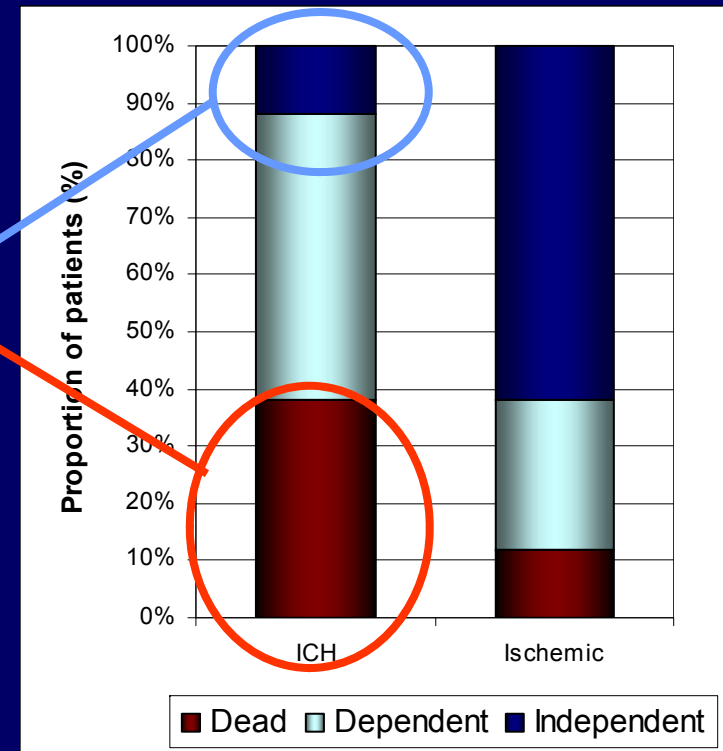


700,000 Total Strokes Annually



ICH associated with high mortality and limited recovery

- **Mortality**
 - 6-month, 30%-50%
 - 1-year, 50%
- **Only 20% of ICH patients are independent at 6 months vs 60% of ischemic stroke patients**
- **Medical costs**
 - US \$125,000 lifetime cost per person (1990)
 - Direct and indirect costs (lost productivity + caregiver burden)



Is there benefit in acutely treating hypertension?

- **INTERACT (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial)**
- **Pilot phase (N=404 patients) to assess feasibility and safety; preliminary efficacy data on hematoma expansion**
- **Acute ICH patients within 6 hours of onset and with SBP >150 mm Hg and <220 mm Hg**

INTERACT

- **404 patients randomized (201 AHA Guideline-based treatment group [target ≤ 180 mm Hg] vs 203 intensive treatment group [target SBP ≤ 140 mm Hg])**
- **172 CT analyses in AHA Guideline-based treatment group and 174 in intensive treatment group**
- **Groups were demographically similar**

AHA Guidelines 2007

- 1. If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 minutes.**
- 2. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is evidence of or suspicion of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications to keep cerebral perfusion pressure >60 to 80 mm Hg.**
- 3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is no evidence of or suspicion of elevated ICP, then consider a modest reduction of blood pressure (eg, MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg) using intermittent or continuous intravenous medications to control blood pressure, and clinically reexamine the patient every 15 minutes.**