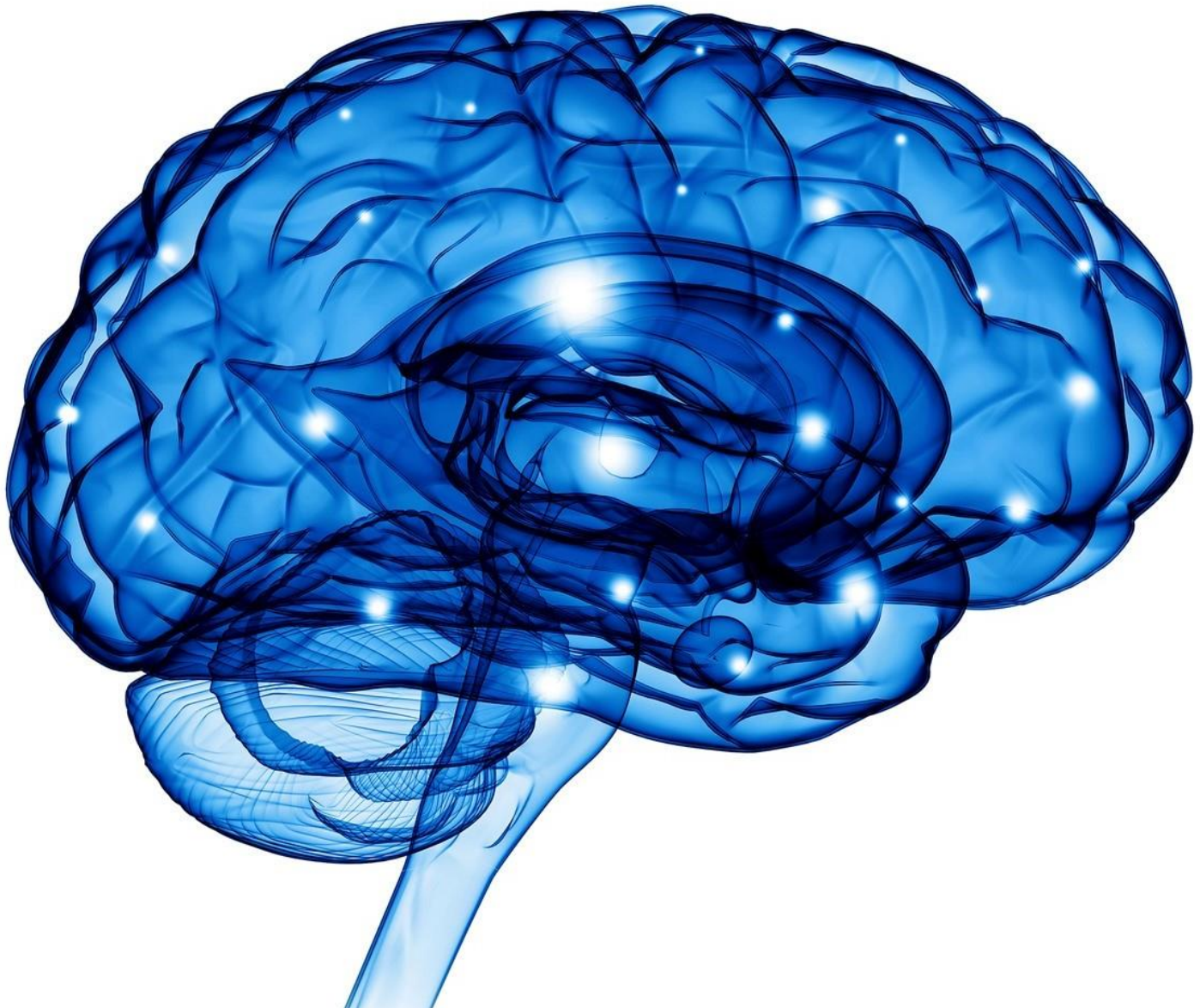

Blood pressure and coagulopathy management in ICH

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Disclosures

- I do not have relevant financial relationships with commercial interests related to the content of this presentation

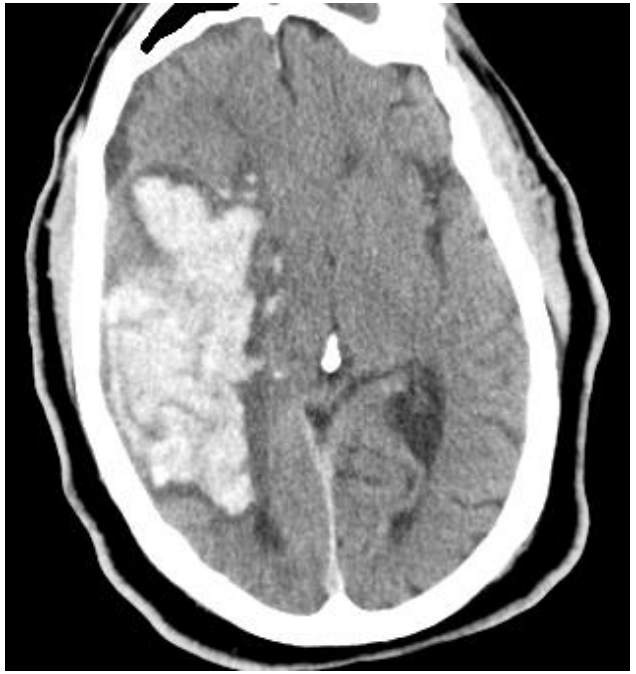
Objectives

1. Evaluate the impact of blood pressure control in ICH
2. Identify coagulopathy related ICH and reversal strategies

Spontaneous ICH

- 10-15% of strokes
- Mortality 30-50%

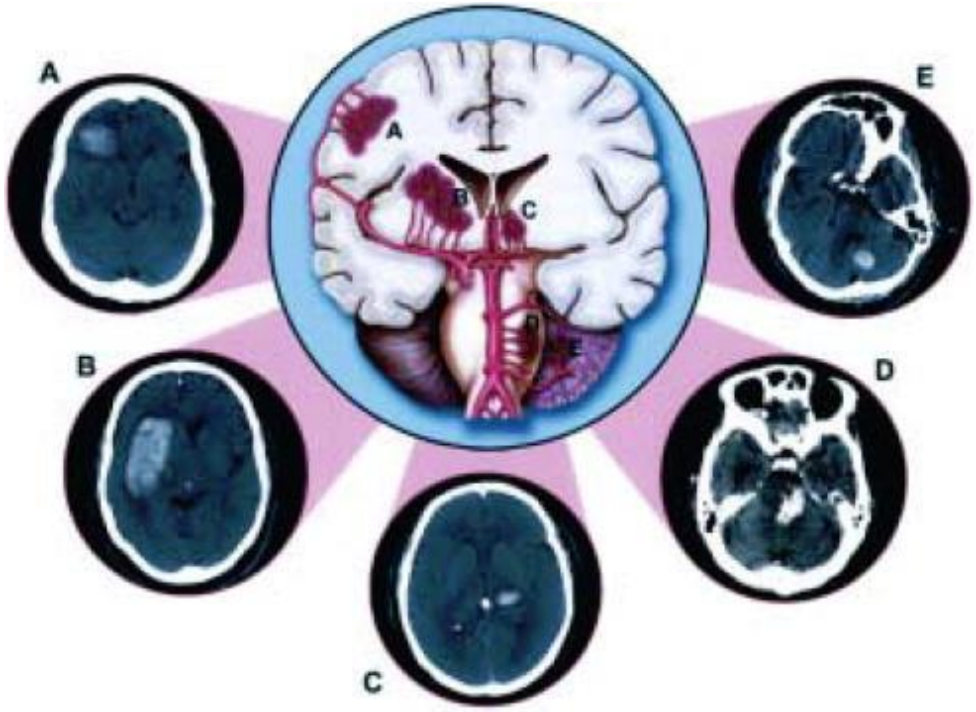
- Risk factors:
  - Hypertension
  - Coagulopathy
  - Amyloid angiopathy
  - Substance abuse, esp. cocaine



Molyneux Lancet 2015.

Location, location, location

Putamen
Thalamus
Pons
Cerebellum

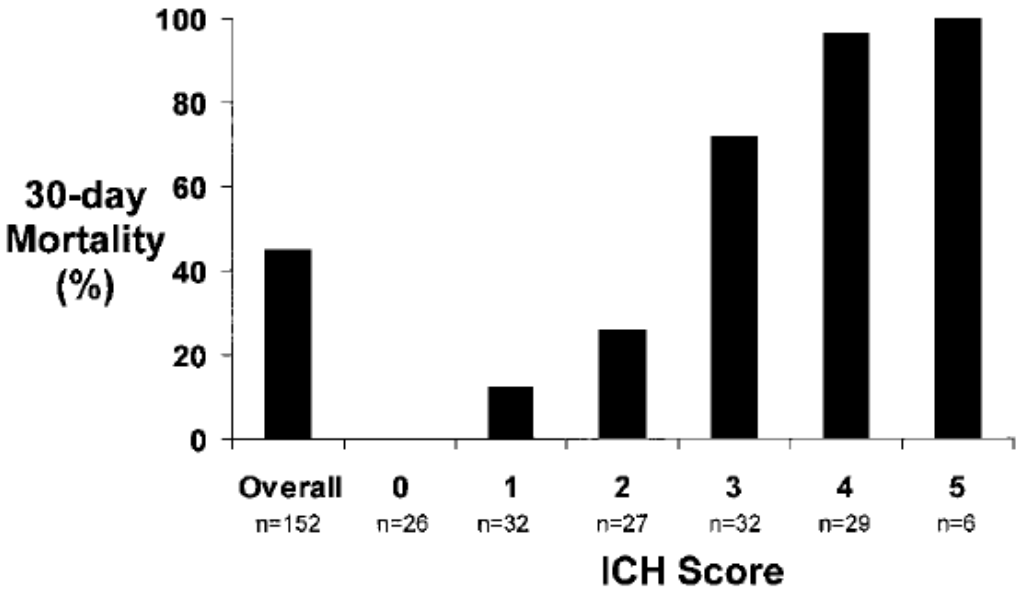


- Larger hematoma volume
  - Lobar, putamen

- Functional outcomes
  - Good: cerebellar, caudate
  - Bad: pontine, multilobar

ICH Score

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



The ICH Score and 30-day mortality. Thirty-day mortality increases as ICH Score increases. No patient with an ICH Score of 0 died. All patients with an ICH Score of 5 died. No patient in the UCSF ICH cohort had an ICH Score of 6, although this would be expected to be associated with mortality.

Hemphill. Stroke, 2001.

Early ICH management

1. Establish blood pressure target
2. Coagulopathy reversal
3. EVD, surgery if indicated

Blood Pressure

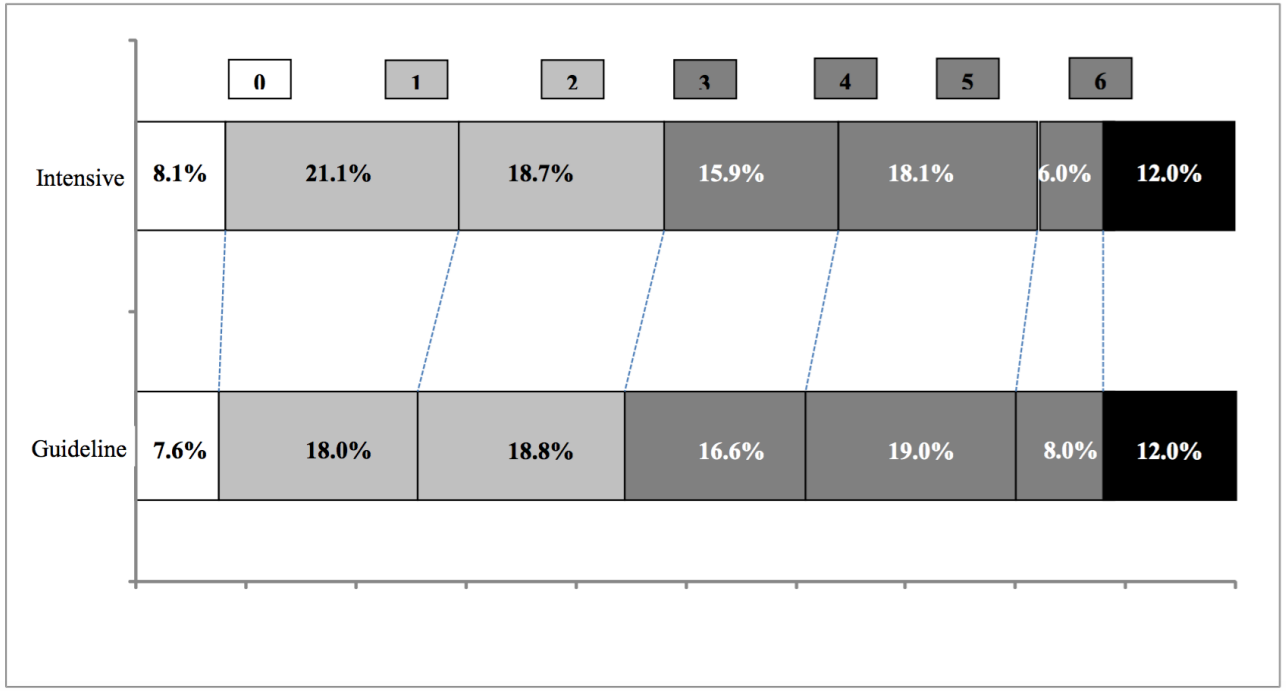
INTERACT2

- 2839 patients, all volumes
- Intensive SBP <140 vs. standard SBP <180 within 6 hours
- No significant difference in poor outcome (mRS 3-6) at 90 days
  - 52% vs. 55.6%
- Ordinal analysis: lower mRS in intensive group
  - OR for disability= 0.87, 95% CI 0.77-1, p=0.04
- No difference in mortality 11.9% vs. 12%

Anderson. NEJM, 2013.

INTERACT2

Figure S3. Distribution of scores on the modified Rankin scale at 90 days showing a 13% reduction in the odds of disability (P=0.044) from early intensive blood pressure lowering



Poor outcome

52%

55.6%

INTERACT2

Supplementary Table S2. Effects of early blood pressure lowering treatments on hematoma volume*

	Blood Pressure Lowering					
	Intensive Group (N = 491)		Guideline Group (N = 473)		Absolute (mL) or proportional (%) decrease in intensive group	
Hematoma volumes					**(95% CI)**	**P Value**
Baseline to 24 hours - ml	Baseline	24 hours	Baseline	24 hours		
Hematoma	15.7±15.7	18.2±19.1	15.1±14.9	20.6±24.9		
Growth of the hematoma volume– ml	24 hours minus baseline		24 hours minus baseline		Guideline minus intensive	
Absolute - mean (95% CI)	3.1 (2.1 to 4.1)		4.9 (3.1 to 6.6)		1.8 (-0.3 to 3.8)	0.091
- adjusted mean (95% CI)†	2.3 (0.2 to 4.4)		3.7 (1.6 to 5.8)		1.4 (-0.6 to 3.4)	0.180
Relative - mean, % (95% CI)	44.7 (10.3 to 79.0)		52.2 (33.5 to 70.8)		7.5 (-31.9 to 47.0)	0.708
- adjusted median, % (95% CI)†	17.2 (9.3 to 25.7)		21.7 (13.5 to 30.5)		4.5 (-3.1 to 12.7)	0.269
Proportion of patients with *substantial* growth of the hematoma						
Hematoma – no. (%)	128 (26.1)		125 (26.4)		0.4 (-5.4 to 6.1)	0.899

*CI denotes confidence intervals. ICC was 0.92 for total volume and 0.95 with extreme outliers removed, for inter-reader reliability checked by re-analysis of 15% of the scans by a single neurologist using intra-class correlation with and without removing outliers in 625 cases.

†Covariates in the adjusted analysis were baseline volume, location and time from onset of ICH to CT scan. 95% CI for difference in adjusted medians were calculated using the bootstrap percentile method. Because of skewed raw data, adjusted medians are reported with 95% CI obtained by back-transformation.

Blood Pressure Management
AHA/ASA Guidelines 2015

BP: Recommendations

1. **For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe *(Class I; Level of Evidence A)* and can be effective for improving functional outcome *(Class IIa; Level of Evidence B)*.** (Revised from the previous guideline)
2. **For ICH patients presenting with SBP >220 mm Hg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring *(Class IIb; Level of Evidence C)*.** (New recommendation)

Hemphill. Stroke, 2015.

ATACH2

The NEW ENGLAND JOURNAL of MEDICINE

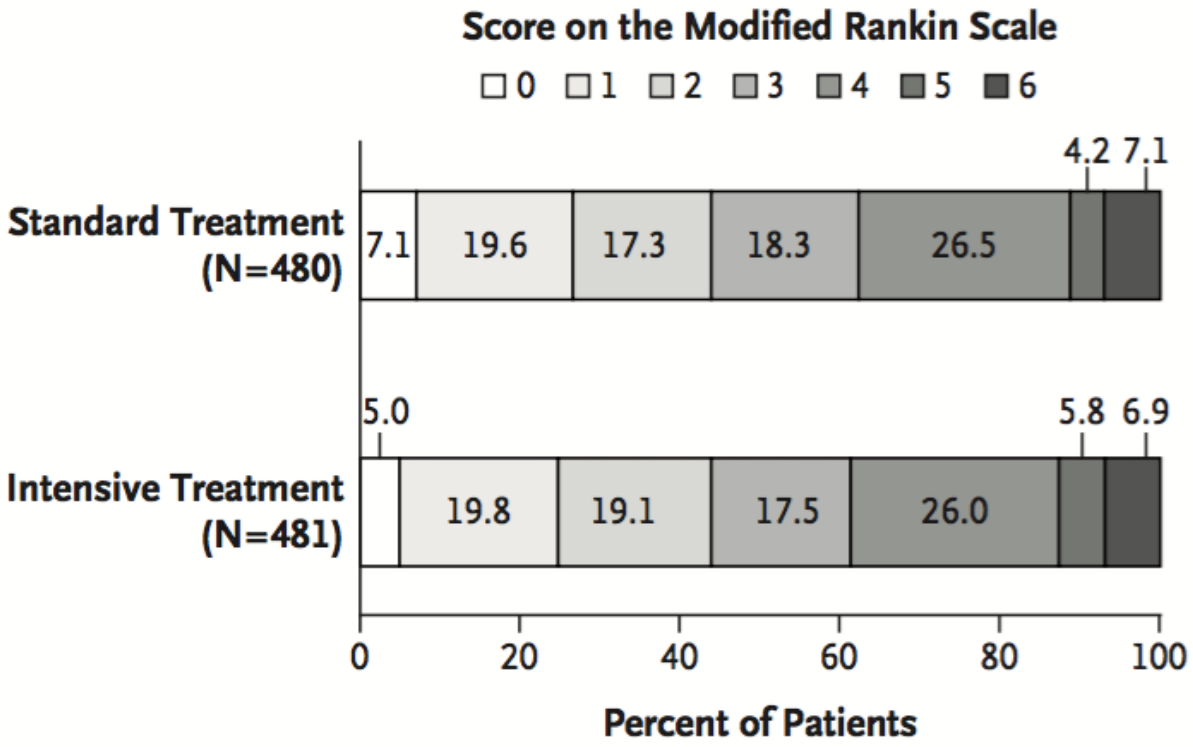
ORIGINAL ARTICLE

Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage

- 1000 patients with ICH volume <60cc
- Intensive SBP 110-140 vs. standard 140-180 within 4.5 hours
- No significant difference in poor outcome (mRS 4-6) at 90 days
  - 38.7% vs. 37.7%
- Overall adverse events similar
- Renal adverse events within 7 days 9% vs. 4%, p=0.002
- Enrollment stopped early for futility

Quereshi. NEJM, 2016.

ATACH2



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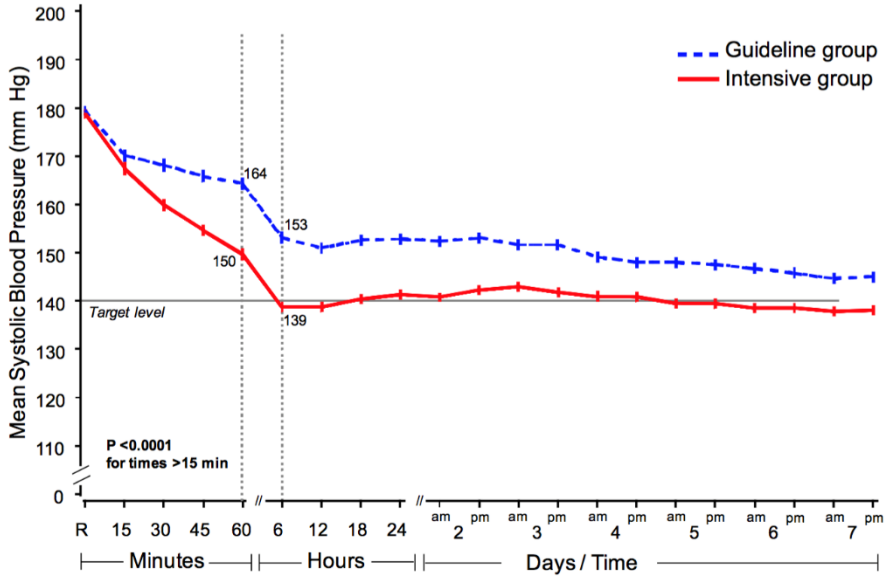
INTERACT2 vs. ATACH2



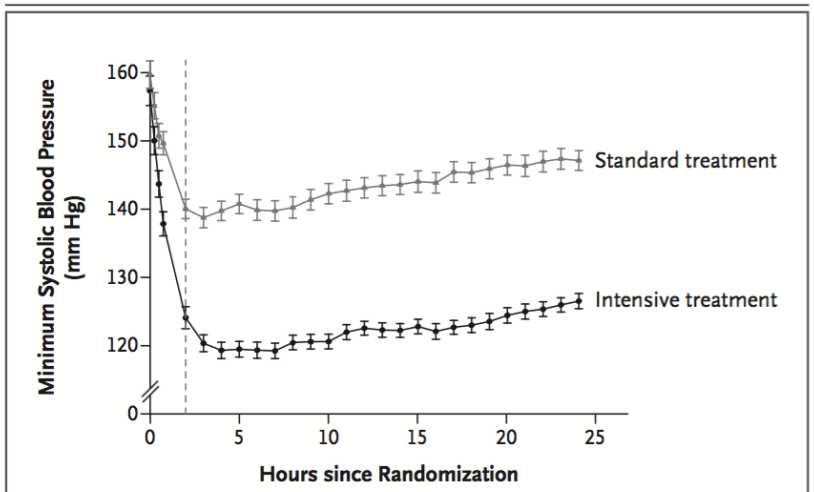


Figure 1. Mean Hourly Minimum Systolic Blood Pressure during the First 24 Hours after Randomization, According to Treatment Group.

The dashed vertical line indicates 2 hours, and I bars 95% confidence intervals.

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Blood pressure does matter

- Timing
- Magnitude of lowering
- BP variability

Ann Neurol 2020; 88:388-395.
Neurocrit Care 2020; 33:689-398.
Neurology 2018; 91:e1058-e1066.

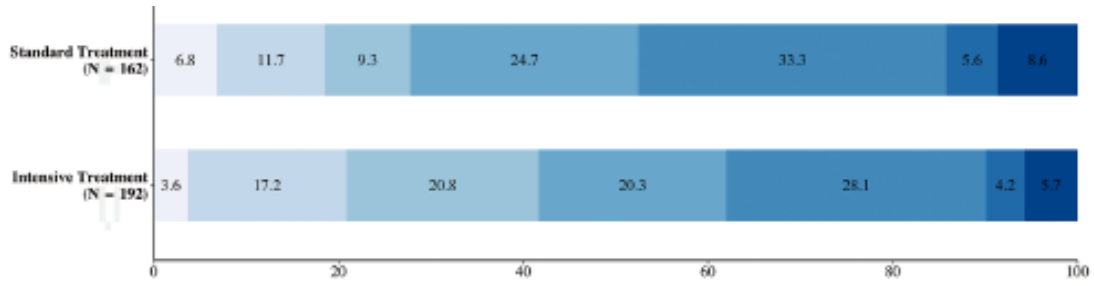
Timing of BP lowering

- Post-hoc analysis of ATACH-2 data
- 354/913 patients treated within 2 hours
  - Reduced hematoma expansion 18.2% vs. 28.4%, p=0.02
  - Increased good functional outcome (mRS 0-2) at 3 months 41.7% vs. 27.8%, p=0.006
  - mRS shift towards better outcome at 3 months

TABLE 3. 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

[a]Adjusted for age, baseline hematoma volume, ethnicity, nicardipine pretreatment before randomization, time from onset to nicardipine, systolic blood pressure before nicardipine, baseline Glasgow Coma Scale score, and intraventricular hemorrhage. CI = confidence interval.



Ann Neurol 2020; 88:388-395.

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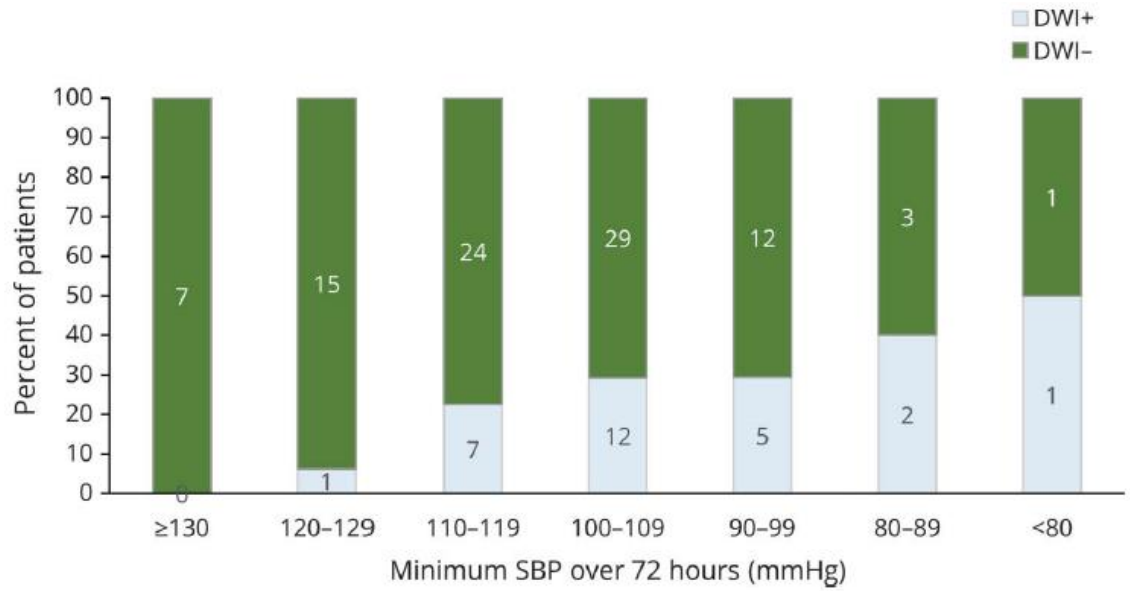
Ultra high BP at presentation

- Post-hoc analysis of ATACH-2 data
- 228/999 patients with initial SBP >220
- Intensive BP lowering
  - Higher neurologic deterioration 24h 15.5% vs. 6.8%
  - No differences in hematoma expansion or 3m death/severe disability
  - Higher rates of kidney adverse events 13.6% vs. 4.2%
- SBP reduction >90mmHg associated with AKI-> positive predictor of mortality

JAMA Neurol 2020; 77:1355-1365.
J Am Heart Assoc 2018; 7:e008439.

Ischemic complications of BP lowering

- DWI+ lesions on MRI
  - Older age, higher admission BP, greater change in MAP, microbleeds, and microvascular white matter disease
  - Poor functional outcome at 90 days
- SBP goal <140 mmHg compared with <160 mmHg (protocol change)
  - Cerebral ischemia (32% vs. 16%, p=0.047)
  - Early neurologic deterioration (19% vs. 5%, p=0.022)



Neurology 2017; 88:782-788.
Neurology 2018; 91:e1058-e1066.

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BPV

- FAST-MAG cohort
- Hyperacute phase (above)
  - 0 to 4-6 hours
- Acute phase (below)
  - 0 to 24-26 hours

SD= standard deviation of SBP

CV= coefficient of variation of SBP

SV= successive variation of SBP

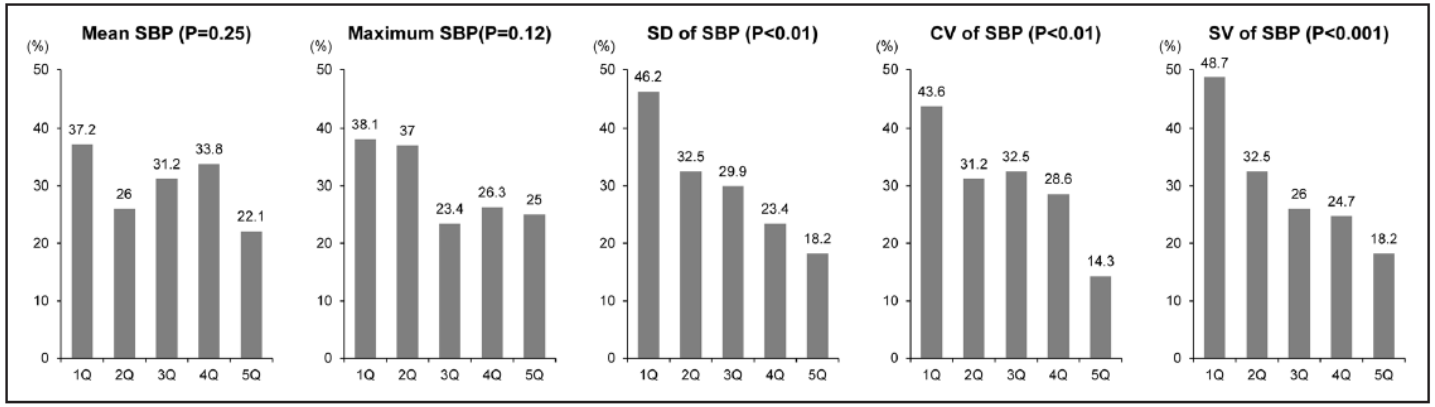

Figure 1. Proportion (as percentage) of patients with favorable outcomes according to quintiles (1Q: lowest quintile group, 5Q: highest quintile group) of each blood pressure variability parameter in the hyperacute period (0 to 4–6 hours after onset). The proportion of patients with favorable outcomes was significantly decreased across the quintiles of SD, coefficient of variation (CV), and successive variation (SV). However, quintiles of maximum systolic blood pressure (SBP) and mean SBP were not correlated with outcome. *P* values are for linear trend.

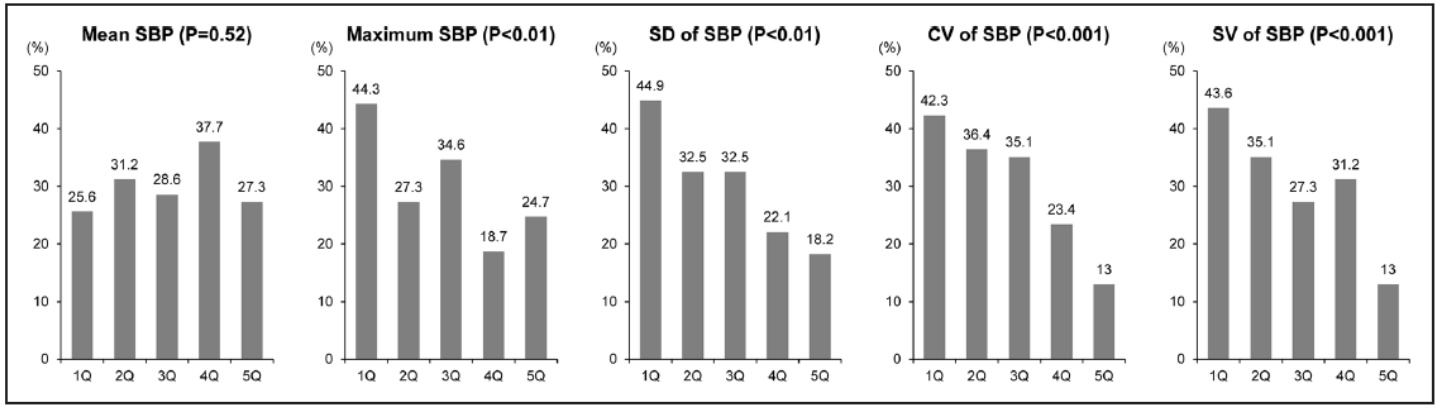

Figure 2. Proportion (as percentage) of patients with favorable outcomes according to quintiles (1Q: lowest quintile group, 5Q: highest quintile group) of each blood pressure variability parameter in the acute period (0 to 24–26 hours after onset). The proportion of patients with favorable outcomes was significantly decreased across the quintiles of SD, coefficient of variation (CV), successive variation (SV), and maximum systolic blood pressure (SBP). However, quintiles of mean SBP were not correlated with outcome. *P* values are for linear trend.

Stroke 2018; 49:348-354.

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AHA/ASA 2022

Recommendations for Acute BP Lowering
Referenced studies that support recommendations are summarized in Data Supplements 16 and 17.

COR	LOE	Recommendation
2a	B-NR	1. 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.[138]
2a	C-LD	2. 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.[139,140]

Recommendations for Acute BP Lowering (Continued)

COR	LOE	Recommendations
2b	B-R	3. In patients with spontaneous ICH of mild to moderate severity presenting with SBP between 150 and 220 mm Hg, acute lowering of SBP to a target of 140 mm Hg with the goal of maintaining in the range of 130 to 150 mm Hg is safe and may be reasonable for improving functional outcomes.[138,141–147]
2b	C-LD	4. 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.[148]
3: Harm	B-R	5. In patients with spontaneous ICH of mild to moderate severity presenting with SBP >150 mm Hg, acute lowering of SBP to <130 mm Hg is potentially harmful.[146,149,150]

Stroke. 2022;53:e282–e361.

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Coagulopathy

Coagulopathy and ICH

- Up to 20% of ICH related to anticoagulant therapy
- Associated with:
  - Lobar location
  - Increased risk of hematoma expansion
  - Poor neurological outcome
  - Mortality
- Anticoagulant use anticipated to increase with aging population

Rosand et al. Arch Int Med, 2004.
Maas et al. Neurocrit Care, 2013.

Anticoagulation reversal

- Discontinue anticoagulants immediately
- Guide warfarin reversal by INR values
  - Re-dose as necessary
- DOAC reversal
  - Obtain information on timing of last dose
  - Treat based on clinical bleeding > lab testing
  - Reverse if within 3-5 half lives of administration
  - Activated charcoal is an option if ingestion within the past 2 hours

Agent	Mechanism	Half-life	Reversal
Warfarin	Reduction in vitamin K-dependent clotting factors (II, VII, IX, X)	20-60 h	Vitamin K 10 mg IV PCC 25-50 U/kg FFP 10-15 ml/kg if PCC not available
Dabigatran	Direct thrombin inhibitor	13 h 22-35 h if ClCr <30	Idarucizumab 5 mg IV x2 doses PCC if idarucizumab not available Hemodialysis
Rivaroxaban, apixaban, edoxaban	Xa inhibitor	Rivaroxaban 7-9 h Apixaban 9-14 h	PCC 50 U/kg Andexanet
Heparin	Indirectly inhibits Xa and IIa via antithrombin	45-90 min	Protamine 1 mg per 100 U heparin given within past 2-3 h
Enoxaparin	Same as heparin but mainly Xa	4 h	Protamine reverses ~60% of effect <8 h: 1 mg per 1 mg enoxaparin 8-12 h: 0.5 mg per 1 mg enoxaparin

Guidelines for Reversal of Antithrombotics in Intracranial Hemorrhage. Neurocrit Care 2016.

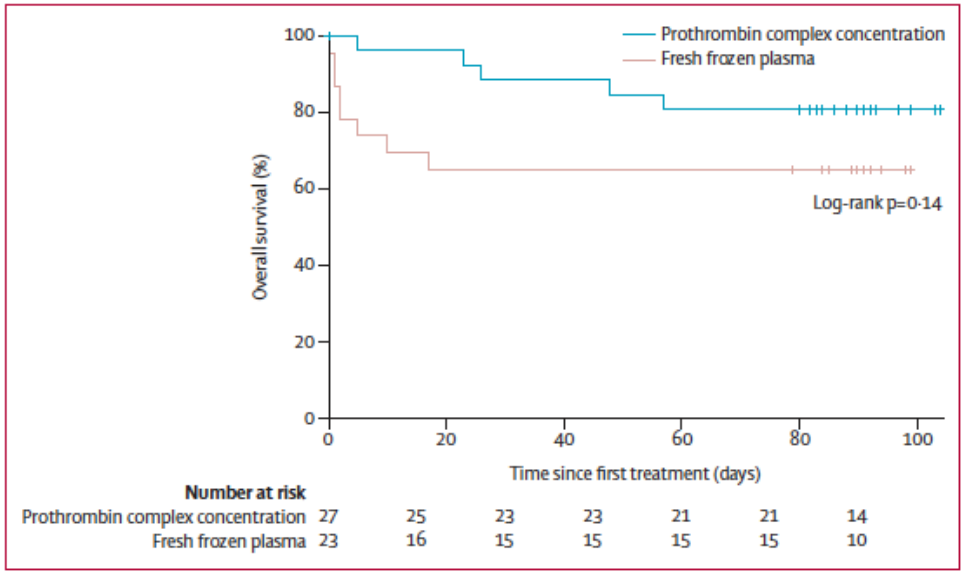
Prothrombin complex concentrate (PCC)

- Derived from plasma
- Contain variable amounts of factors II, VII, IX, X
  - Activated formulations available
- Fast prep time
- Rapid INR correction with smaller volume
- Cost: ~$5000 per dose

Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial

- 54 patients
- Primary outcome: INR <1.2 within 3h of treatment
  - FFP 9% vs. PCC 67% (p=0.0003)
- Hematoma expansion >=33%
  - FFP 59% vs. PCC 44% (p=0.024)
- PCC treatment effect: 16.9cc less hemorrhage expansion

- *Discontinued early due to safety concerns*



Steiner T, et al. Lancet Neurol 2016.

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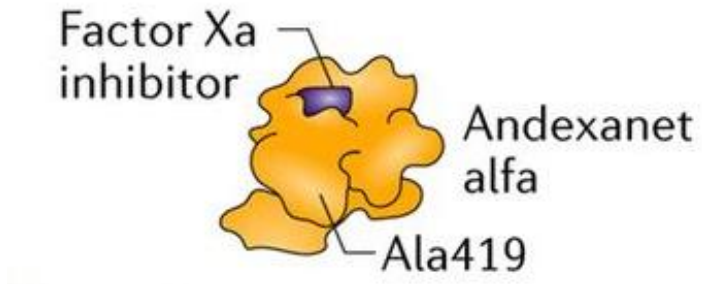
Andexanet alpha

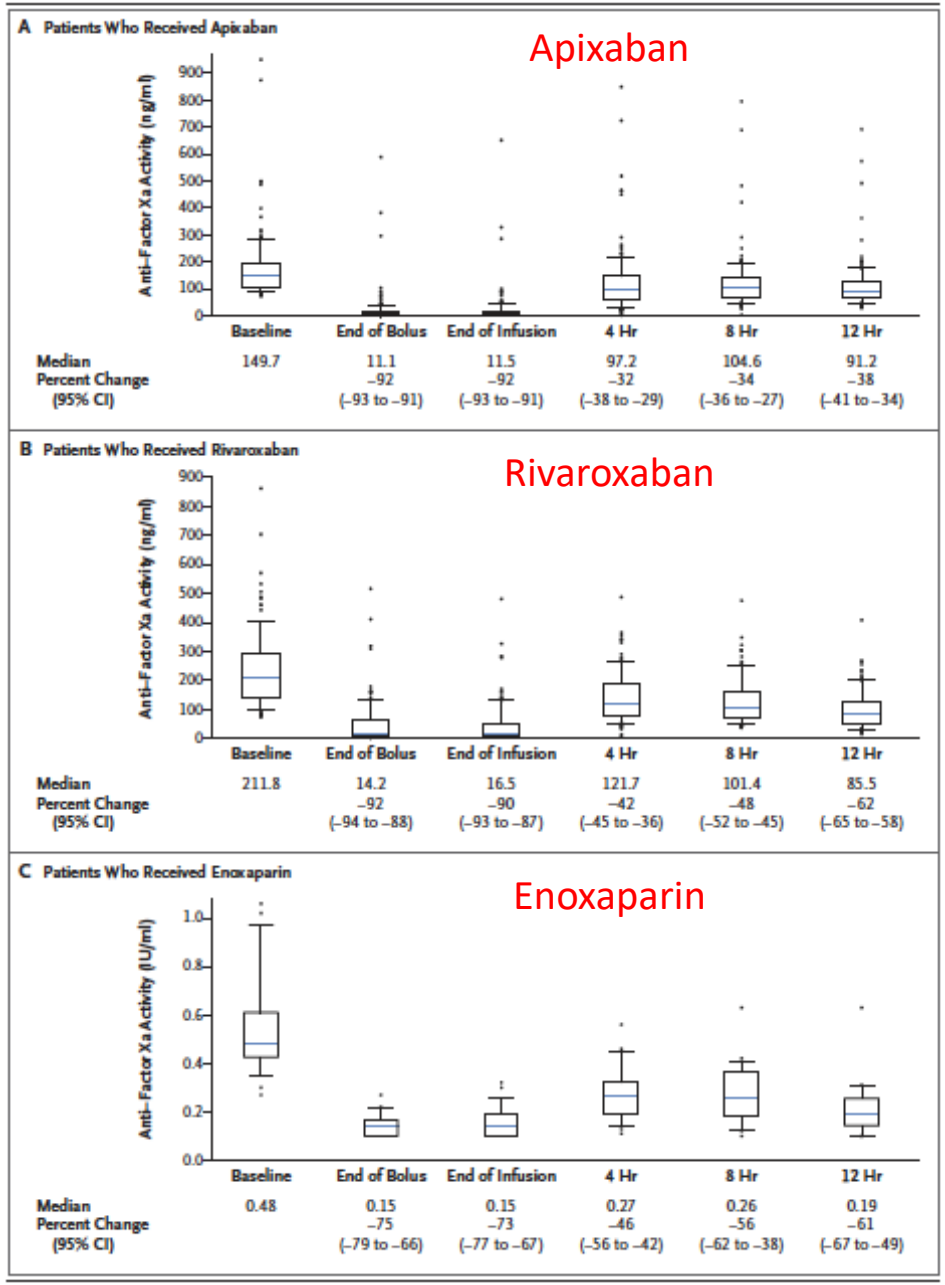


- Modified recombinant inactive Xa
- Binds and sequesters Xa inhibitors
- Reduces anti-Xa activity
- Approved by FDA May 2018 for reversal of apixaban and rivaroxaban
  - Life threatening or uncontrolled bleeding

- Expensive! $25-50k per patient

Levy JH, Douketis J, Weitz JI. Nat Rev Cardiol 2018.

Anti-Xa Activity



Connolly SJ, et al. New Engl J Med 2019.

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RESEARCH Open Access

Andexanet alfa versus four-factor prothrombin complex concentrate for the reversal of apixaban- or rivaroxaban-associated intracranial hemorrhage: a propensity score-overlap weighted analysis

Olivia S. Costa[1,2], Stuart J. Connolly[3,4], Mukul Sharma[3,4], Jan Beyer-Westendorf[5], Mary J. Christoph[6], Belinda Lovelace[6] and Craig I. Coleman[1,2*]

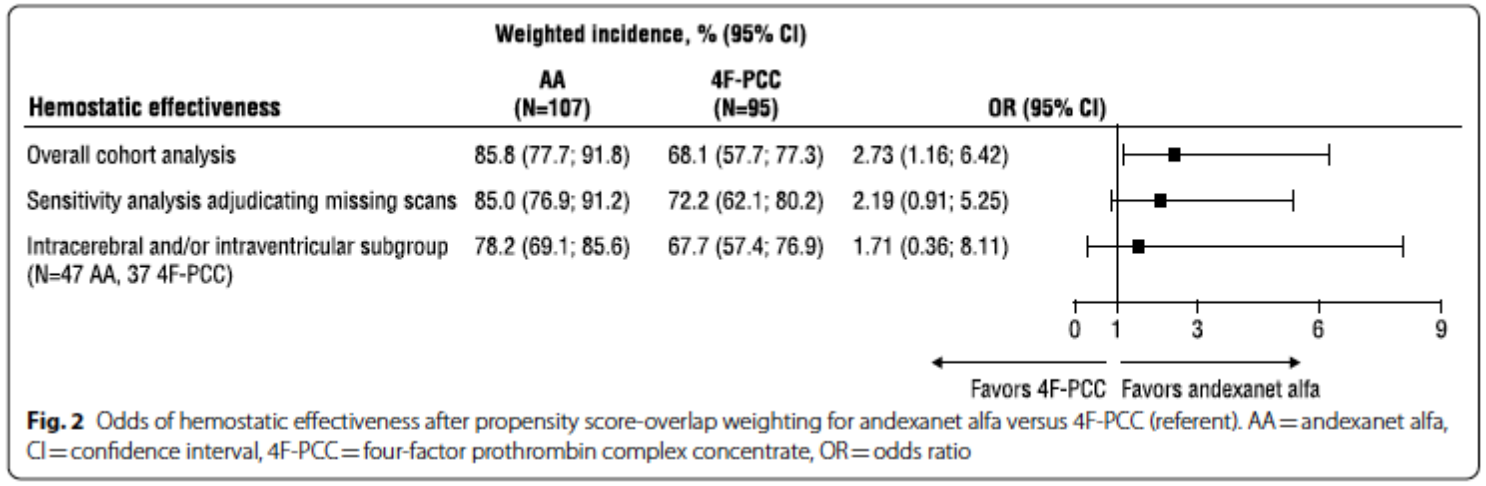

Fig. 2 Odds of hemostatic effectiveness after propensity score-overlap weighting for andexanet alfa versus 4F-PCC (referent). AA = andexanet alfa, CI = confidence interval, 4F-PCC = four-factor prothrombin complex concentrate, OR = odds ratio

Table 4 Volume change between initial and repeat scan for intracerebral and/or intraventricular bleed subpopulation after propensity score-overlap weighting

	Andexanet alfa *n* = 47	4F-PCC *n* = 37
Initial volume (mL), mean ± SD	7.29 ± 9.82	7.29 ± 9.05
Repeat volume (mL), mean ± SD	8.12 ± 12.28	12.02 ± 16.82
Change in volume (mL), mean ± SD	0.83 ± 4.25	4.73 ± 12.10
Weighted difference in mean volume change (mL), 4F-PCC referent (95% CI)	−3.90 (−10.81 to 3.00)	

CI = confidence interval, 4F-PCC = four-factor prothrombin complex concentrate, SD = standard deviation

Crit Care. 2022 Jun 16;26(1):180.

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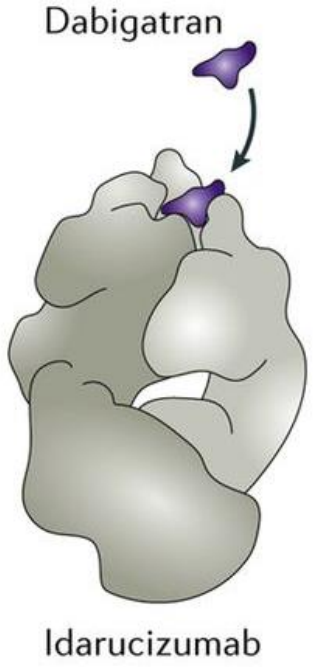
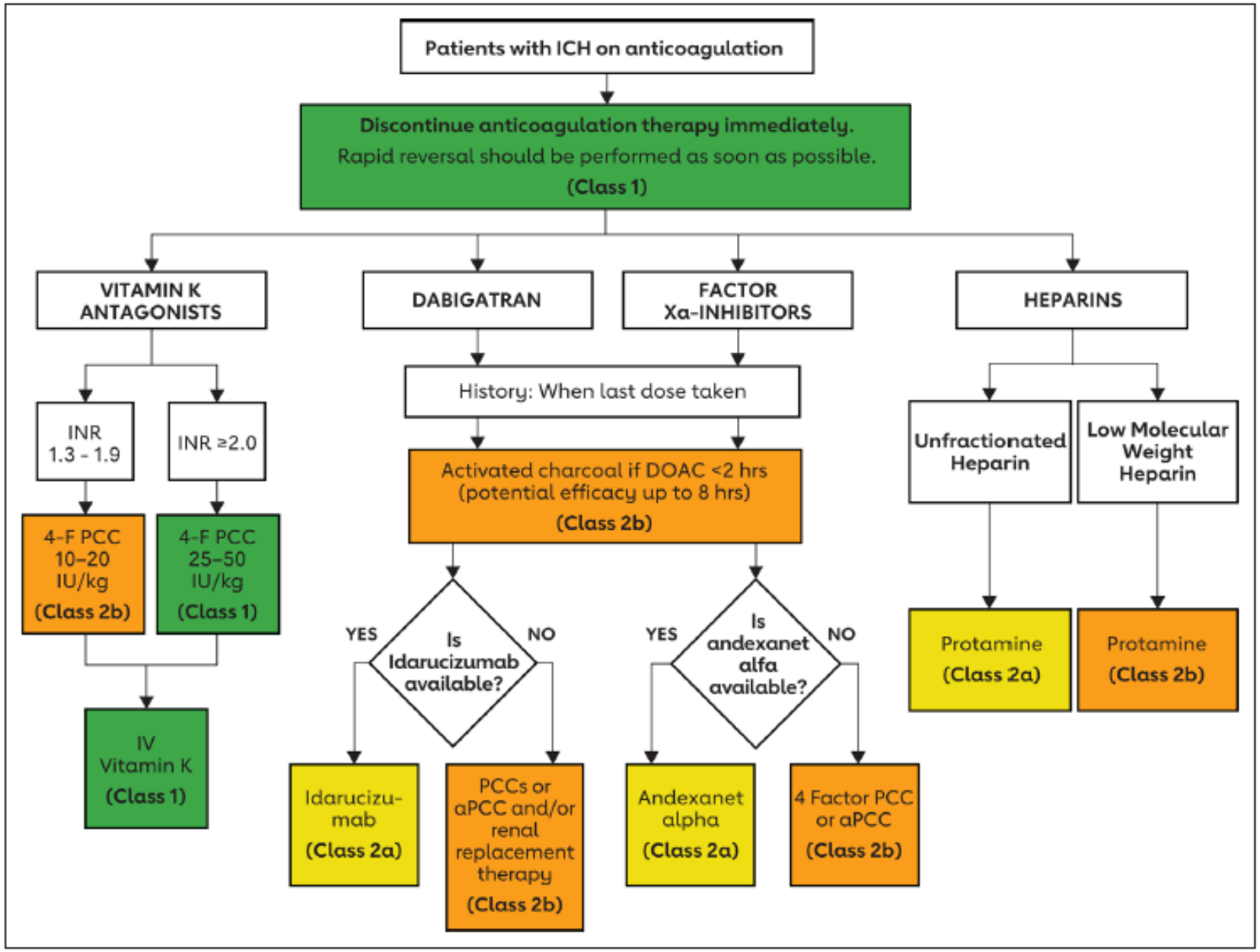
Idarucizumab

- Monoclonal antibody
- High affinity binding to dabigatran
  - 350x higher affinity than dabigatran to thrombin
- Theoretically, no inherent anticoagulant or prothrombotic effects
- Dosing: 5gm= 2 x 2.5gm vials <15 min apart
- Cost: $3500-4000



Levy JH, Douketis J, Weitz JI. Nat Rev Cardiol 2018.



Stroke. 2022;53:e282–e361.

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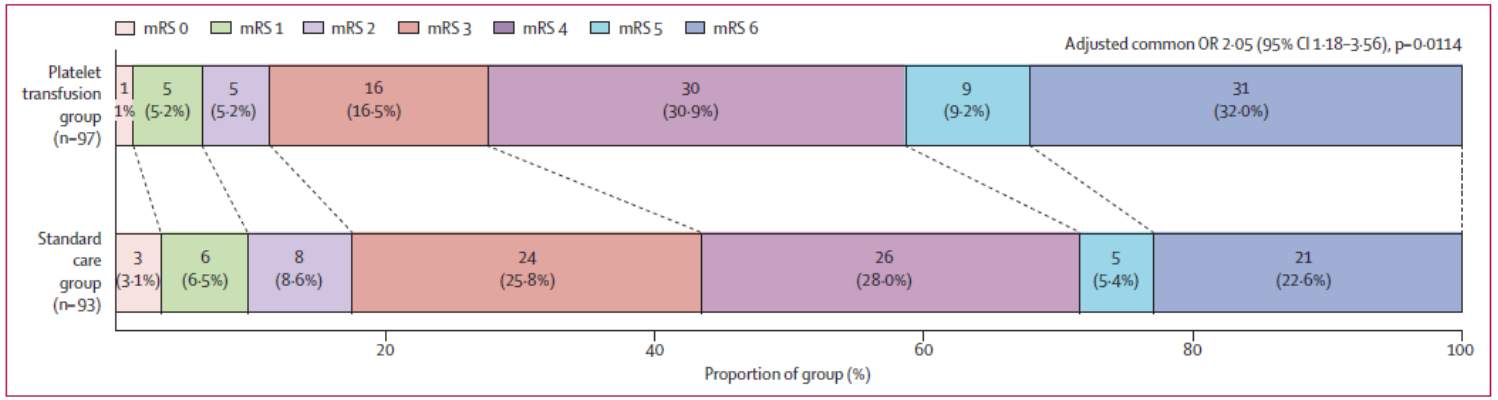
PATCH

- 190 supratentorial ICH
- Antiplatelet use by history
- Platelet transfusion within 90 mins diagnostic CT
- Surgical patients excluded

	Platelet transfusion group (n=97)	Standard care group (n=93)	Odds ratio (95%CI)	p value
Alive at 3 months (survival)	66 (68%)	72 (77%)	0·62 (0·32–1·19)	0·15
mRS score 4–6 at 3 months	70 (72%)	52 (56%)	2·04 (1·12–3·74)	0·0195
mRS score 3–6 at 3 months	86 (89%)	76 (82%)	1·75 (0·77–3·97)	0·18
Median ICH growth at 24 h (mL)*	2·01 (0·32–9·34)	1·16 (0·03–4·42)	..	0·81

Data are n (%) or median (IQR). mRS=modified Rankin Scale. ICH=intracerebral haemorrhage. *n=80 in platelet transfusion group and 73 in standard care group.

Table 2: Secondary outcomes in the intention-to-treat population



Poor outcome

72%

56%

Baharoglu. Lancet, 2016.

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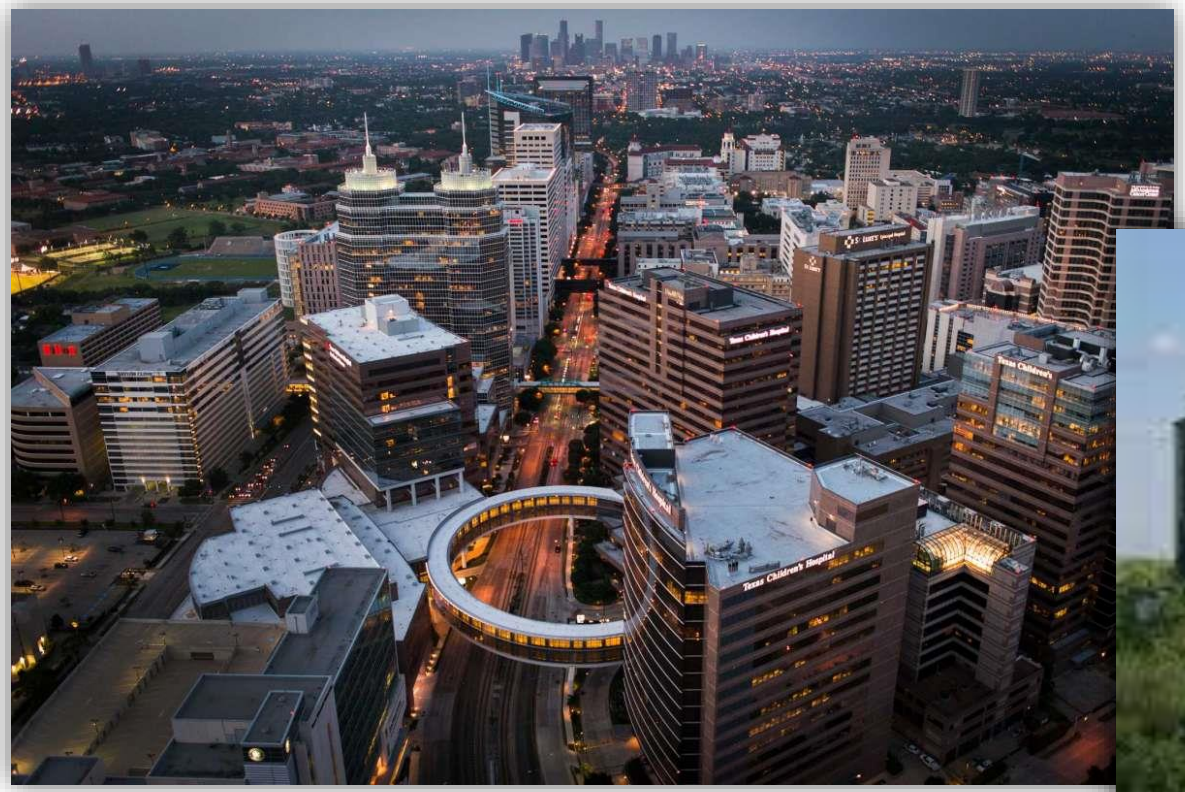
Conclusions

- Blood pressure management is important
- Individualize your blood pressure target and avoid variability
- Identify and reverse coagulopathy as quickly as possible
- Avoid empiric platelet transfusion in non-surgical patients on antiplatelet agents

Thank you!



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