RICORS-ICTUS | Instituto de Salud Carlos III

Time is brain! in intracerebral hemorrhage

Prof. David Rodriguez-Luna, MD, PHD

Department of Neurology, Vall d'Hebron University Hospital, Barcelona

Stroke Research Group, Vall d'Hebron Research Institute, Barcelona

Department of Medicine, Autonomous University of Barcelona, Barcelona

Vall d'Hebron Barcelona Hospital Campus | Vall d'Hebron Hospital Universitari | Vall d'Hebron Institut de Recerca | UAB Universitat Autònoma de Barcelona

david.rodriguez@vallhebron.cat

Disclosures

Funding: AstraZeneca, Sanofi

Speaker bureau: AstraZeneca, Amgen

Consulting: AstraZeneca, Medical Science Consulting (MSC)

Intracerebral hemorrhage

Major public health problem

- Second most common cause of stroke
- Deadliest stroke subtype:
  - 40% pt deceased at one-month
  - 75% pt severely disabled or deceased after the first year

Neurological deterioration occurs frequently

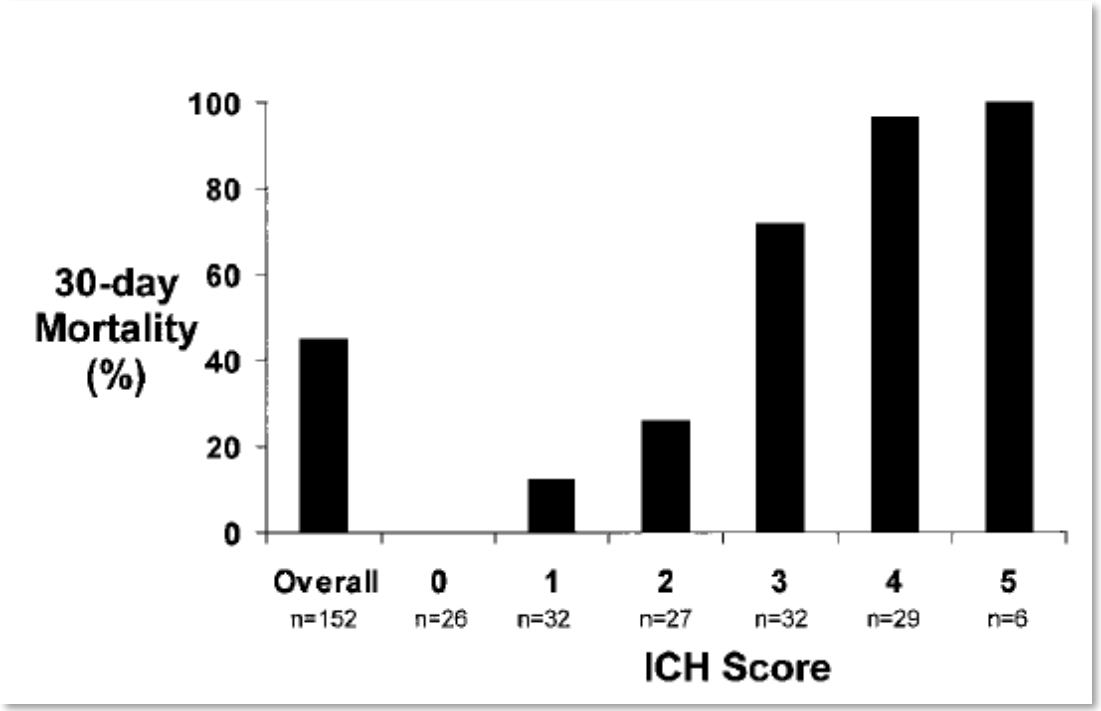
- Need of effective therapies
- Different treatment approaches have the potential to improve outcomes

Prognostic factors

TABLE 3. Determination of the ICH Score

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

GCS score indicates GCS score on initial presentation (or after resuscitation); ICH volume, volume on initial CT calculated using *ABC*/2 method; and IVH, presence of any IVH on initial CT.



Hemphill III et al. Stroke. 2001; 32: 891–897

ICH volume on admission and clinical outcome

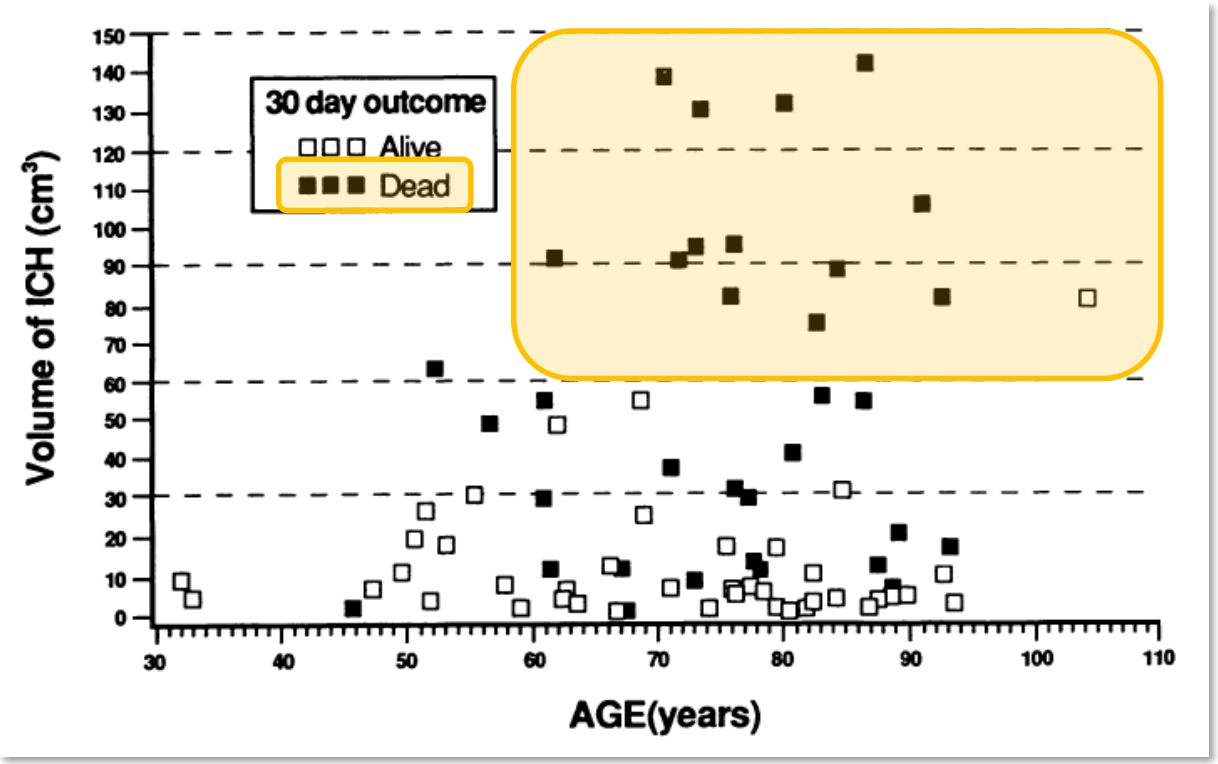
ICH volume on admission is a powerful predictor of neurologic deterioration and mortality

Neurologic deterioration in noncomatose patients with supratentorial intracerebral hemorrhage

Stephan A. Mayer, MD; Ralph L. Sacco, MS, MD; Tianying Shi, MS; and J.P. Mohr, MD

Article abstract—*Objective.* To determine the frequency, time course, and predictors of neurologic deterioration (ND) in noncomatose patients with supratentorial intracerebral hemorrhage (ICH). *Background.* Patients with worsening ICH may benefit from therapy aimed at reducing mass effect due to active bleeding or cerebral edema. *Methods.* We analyzed 46 noncomatose (Glasgow Coma Scale [GCS] score ≥8) patients with ICH in the Stroke Data Bank (SDB). All subjects were examined within 24 hours of onset (mean, 13.6 hours) and were prospectively followed with serial examinations during hospitalization. ND was defined as (1) a ≥2-point decrease in the GCS score, (2) a ≥1-point increase in the SDB weakness score, or (3) a new deficit, unrelated to medical or surgical complications. *Results.* ND occurred in 15 of 46 patients (33%). The frequency of ND was greatest on the first hospital day (eight of 15 patients) and decreased progressively thereafter. Patients with ND had larger hemorrhages (mean volume, 45 ml versus 16 ml, $p < 0.01$) and more frequently demonstrated marked mass effect (60% versus 19%, $p < 0.01$) on initial CT than those with stable deficits, but did not differ with regard to mean GCS score, mean blood pressure, or other clinical variables on admission. Hematoma enlargement was judged to be the cause of worsening in four of 15 (27%) patients. Thirty-day case fatality was 47% in those with ND compared with 3% in those with stable deficits ($p = 0.001$). *Conclusions.* ND occurs in one-third of noncomatose patients with supratentorial ICH and carries a poor prognosis. Large hematoma volume on CT, rather than clinical predictors, identifies patients at high risk for subsequent worsening.

NEUROLOGY 1994;44:1379-1384



Broderick et al. Stroke. 1993; 24: 987–993

ICH due to cerebral small vessel disease

Spontaneous rupture of a damaged vessel (arteriolosclerosis, cerebral amyloid angiopathy)

↓

Hematoma expansion

Increase of ICH volume

Intraventricular (deep) and subarachnoid (lobar) extension

↓

Direct pressure effects: ↑ ICP, hydrocephalus, herniation

Secondary injury: edema, inflammation, biochemical toxicity

Hematoma expansion after hospital admission

Early neurologic deterioration in intracerebral hemorrhage

Predictors and associated factors

R. Leira, MD, PhD; A. Dávalos, MD, PhD; Y. Silva, MD; A. Gil-Peralta, MD, PhD; J. Tejada, MD, PhD; M. Garcia, MD, PhD; J. Castillo, MD, PhD; for the Stroke Project, Cerebrovascular Diseases Group of the Spanish Neurological Society

Abstract—*Objective:* To identify potential predictors of and factors associated with early neurologic deterioration (END) in primary intracerebral hemorrhage (ICH). *Methods:* Two hundred sixty-six patients with spontaneous supratentorial ICH admitted within 12 hours of stroke onset were investigated in a multicenter, prospective study. Sixty-one clinical, biochemical, and neuroimaging variables were registered on admission, and 37 clinical and neuroimaging variables were registered at 48 hours. The volumes of the ICH and peripheral edema on admission and at 48 hours were measured on CT scan. Stroke severity and functional outcome were evaluated with the Canadian Stroke Scale (CSS) and modified Rankin Scale. END was diagnosed when the CSS score decreased ≥1 points between admission and 48 hours. With use of logistic regression analyses, baseline variables that predicted END and factors measured after the early acute phase and associated with END were investigated. *Results:* END occurred in 61 (22.9%) patients. Body temperature of >37.5 °C (odds ratio [OR] 24.5; 95% CI 4.8 to 125), neutrophil count (by 1,000-unit increase; OR 2.1; 95% CI 1.6 to 2.6), and serum fibrinogen levels of >523 mg/dL (OR 5.6; 95% CI 1.9 to 16.2) on admission were independent predictors of END. Among the factors recorded at 48 hours, early ICH growth (OR 4.3; 95% CI 1.3 to 14.5), intraventricular bleeding (OR 2.6; 95% CI 1.4 to 5.0), and highest systolic blood pressure (by 10-unit increase; OR 1.17; 95% CI 1.02 to 1.32) were associated with END in multivariate analyses. *Conclusions:* Clinical and biologic markers of the inflammatory reaction on admission are predictors of subsequent END, whereas early ICH growth, intraventricular bleeding, and high systolic blood pressure within 48 hours are factors associated with END in patients with spontaneous ICH.

NEUROLOGY 2004;63:461–467

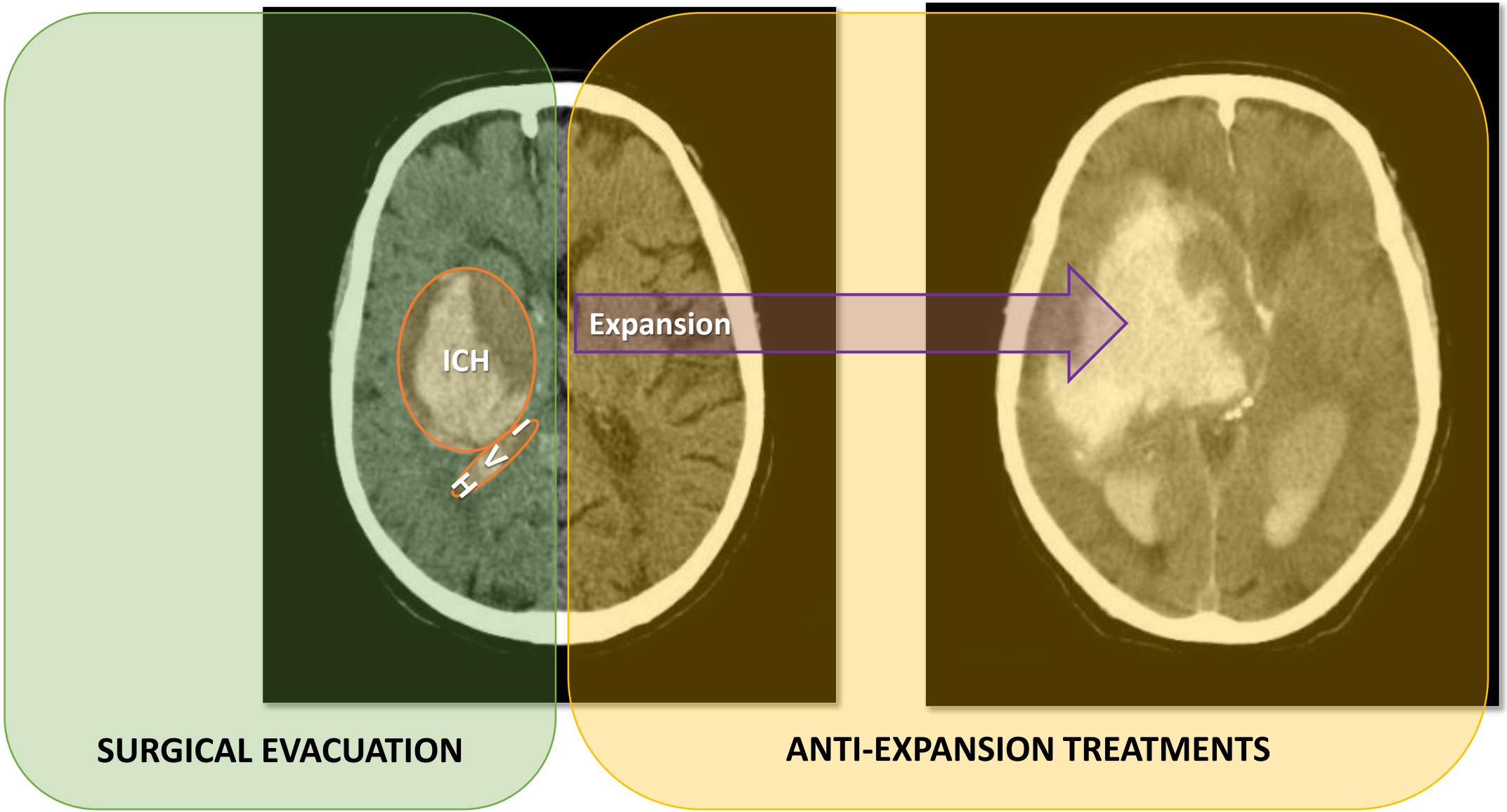
Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage

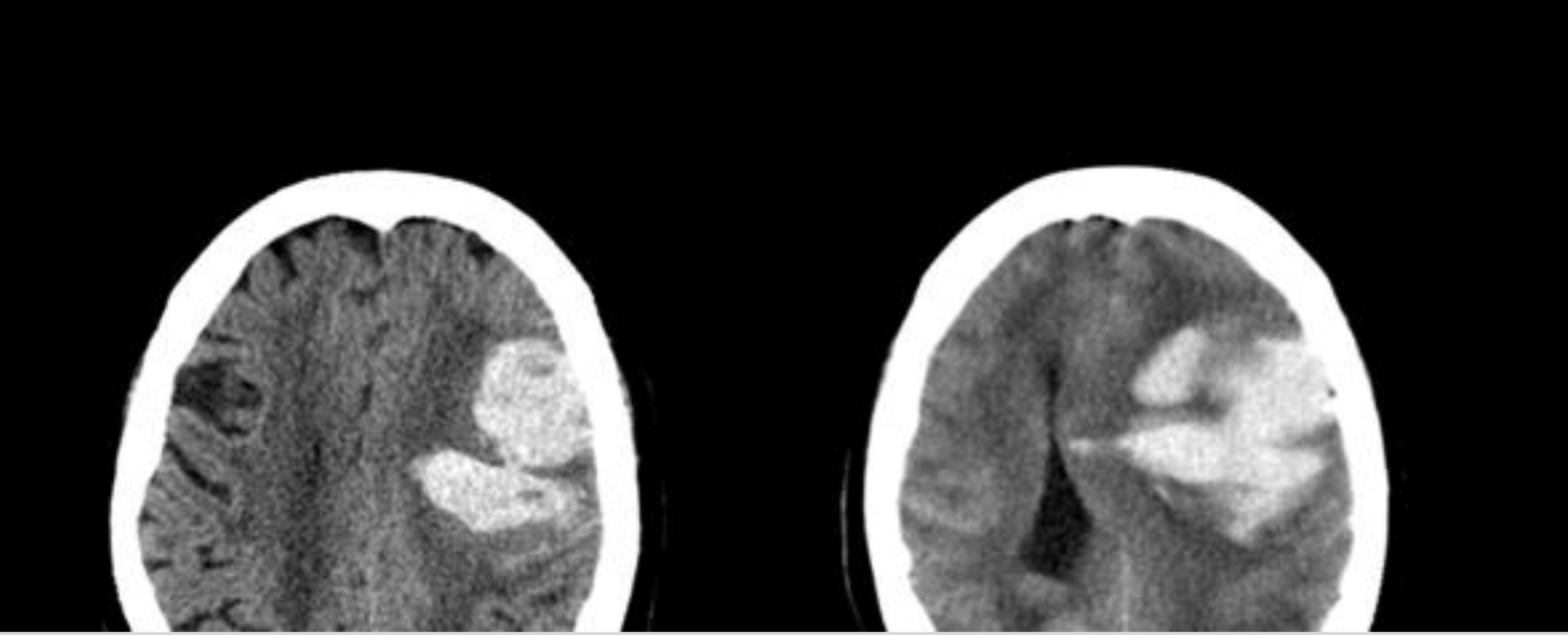
S.M. Davis, MD; J. Broderick, MD; M. Hennerici, MD; N.C. Brun, MD; M.N. Diringer, MD; S.A. Mayer, MD; K. Begtrup, MSc; and T. Steiner, MD, for the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators

Abstract—*Background:* Although volume of intracerebral hemorrhage (ICH) is a predictor of mortality, it is unknown whether subsequent hematoma growth further increases the risk of death or poor functional outcome. *Methods:* To determine if hematoma growth independently predicts poor outcome, the authors performed an individual meta-analysis of patients with spontaneous ICH who had CT within 3 hours of onset and 24-hour follow-up. Placebo patients were pooled from three trials investigating dosing, safety, and efficacy of rFVIIa (n = 115), and 103 patients from the Cincinnati study (total 218). Other baseline factors included age, gender, blood glucose, blood pressure, Glasgow Coma Score (GCS), intraventricular hemorrhage (IVH), and location. *Results:* Overall, 72.9% of patients exhibited some degree of hematoma growth. Percentage hematoma growth (hazard ratio [HR] 1.05 per 10% increase [95% CI: 1.03, 1.08; $p < 0.0001$]), initial ICH volume (HR 1.01 per mL [95% CI: 1.00, 1.02; $p = 0.003$]), GCS (HR 0.88 [95% CI: 0.81, 0.96; $p = 0.003$]), and IVH (HR 2.23 [95% CI: 1.25, 3.98; $p = 0.007$]) were all associated with increased mortality. Percentage growth (cumulative OR 0.84 [95% CI: 0.75, 0.92; $p < 0.0001$]), initial ICH volume (cumulative OR 0.94 [95% CI: 0.91, 0.97; $p < 0.0001$]), GCS (cumulative OR 1.46 [95% CI: 1.21, 1.82; $p < 0.0001$]), and age (cumulative OR 0.95 [95% CI: 0.92, 0.98; $p = 0.0009$]) predicted outcome modified Rankin Scale. Gender, location, blood glucose, and blood pressure did not predict outcomes. *Conclusions:* Hematoma growth is an independent determinant of both mortality and functional outcome after intracerebral hemorrhage. Attenuation of growth is an important therapeutic strategy.

NEUROLOGY 2006;66:1175–1181

Therapeutic targets





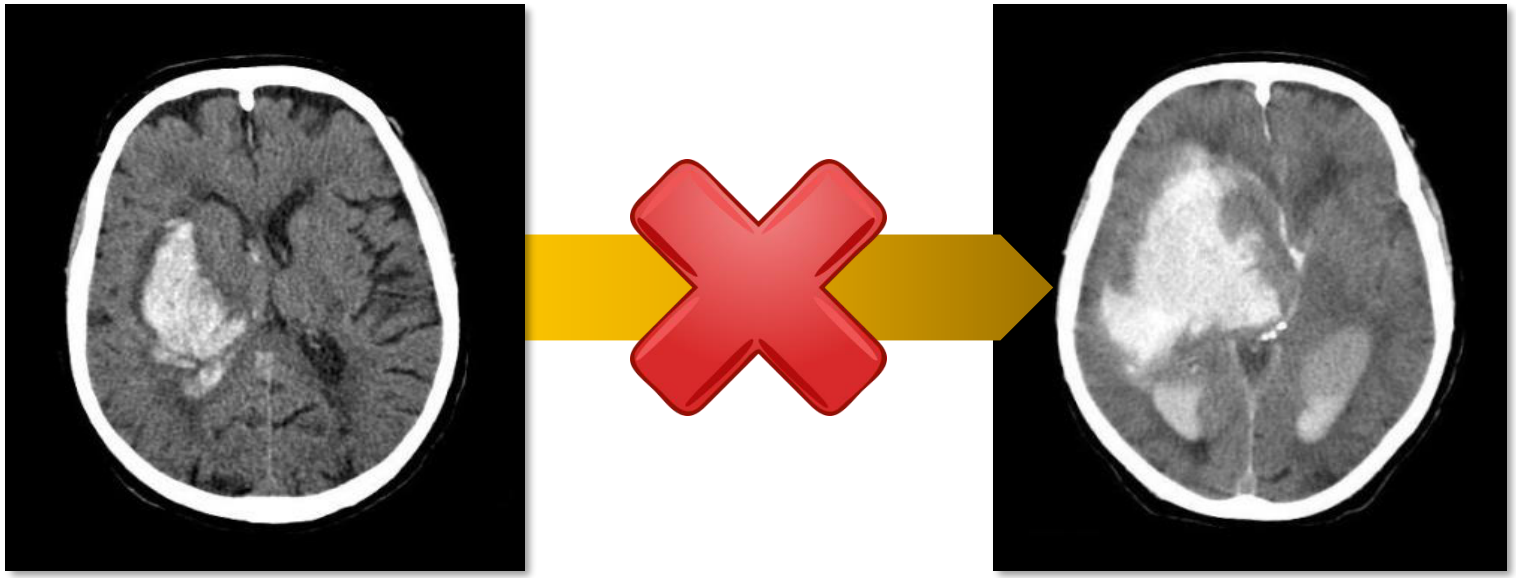
Hematoma Expansion

Hematoma expansion

Potentially modifiable determinant of poor outcome in acute ICH

Key target for emerging therapies

Success of treatments will likely depend on the accurate selection of patients at risk for expansion



Time to imaging is essential when assessing ICH

All ICHs expand! Ability to detect expansion will depend on the timing of the neuroimaging

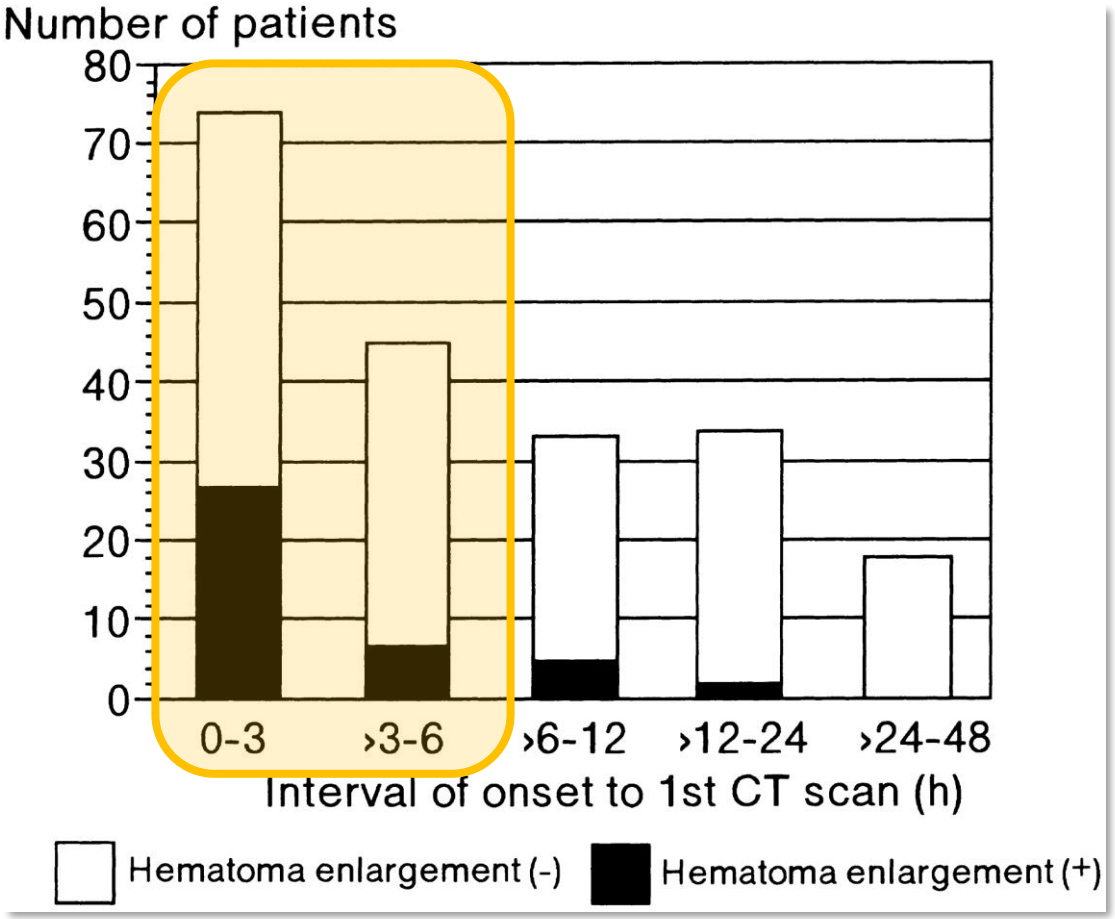
Relationship between the incidence of hematoma growth and time after onset

Time After Onset (hrs)	Hematoma Growth		Total No. of Cases	Incidence of Growth*	Systolic Blood Pressure (mm Hg)†
	Yes	No			
0–1	35	99	134	26.1%	189 ± 37
>1–2	13	75	88	14.8%	181 ± 36
>2–4	8	81	89	9.0%	174 ± 33
>4–6	3	31	34	8.8%	176 ± 34
>6	1	73	74	1.4%	162 ± 27
totals	60	359	419	14.3%	

* There was a significant decrease in the incidence of hematoma growth with time after onset (Cochran-Armitage's method).

† Systolic blood pressure decreased significantly with time after onset (linear regression analysis). Data are presented as mean ± standard deviation.

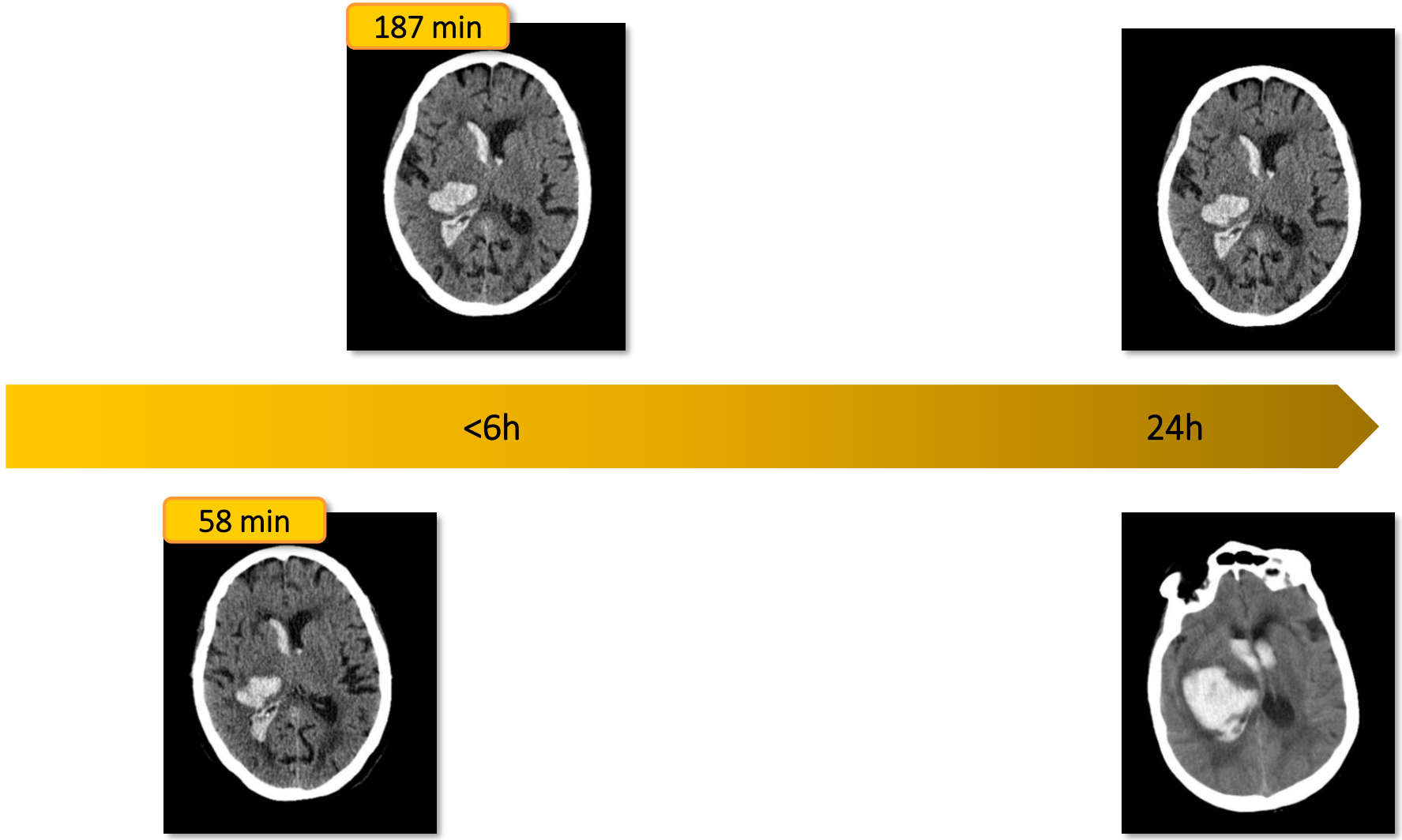
Fujii et al. *J Neurosurg*. 1994; 80: 51–57



Kazui et al. *Stroke*. 1996; 27: 1783–1787

ICH volume is a “single snapshot” of a dynamic process

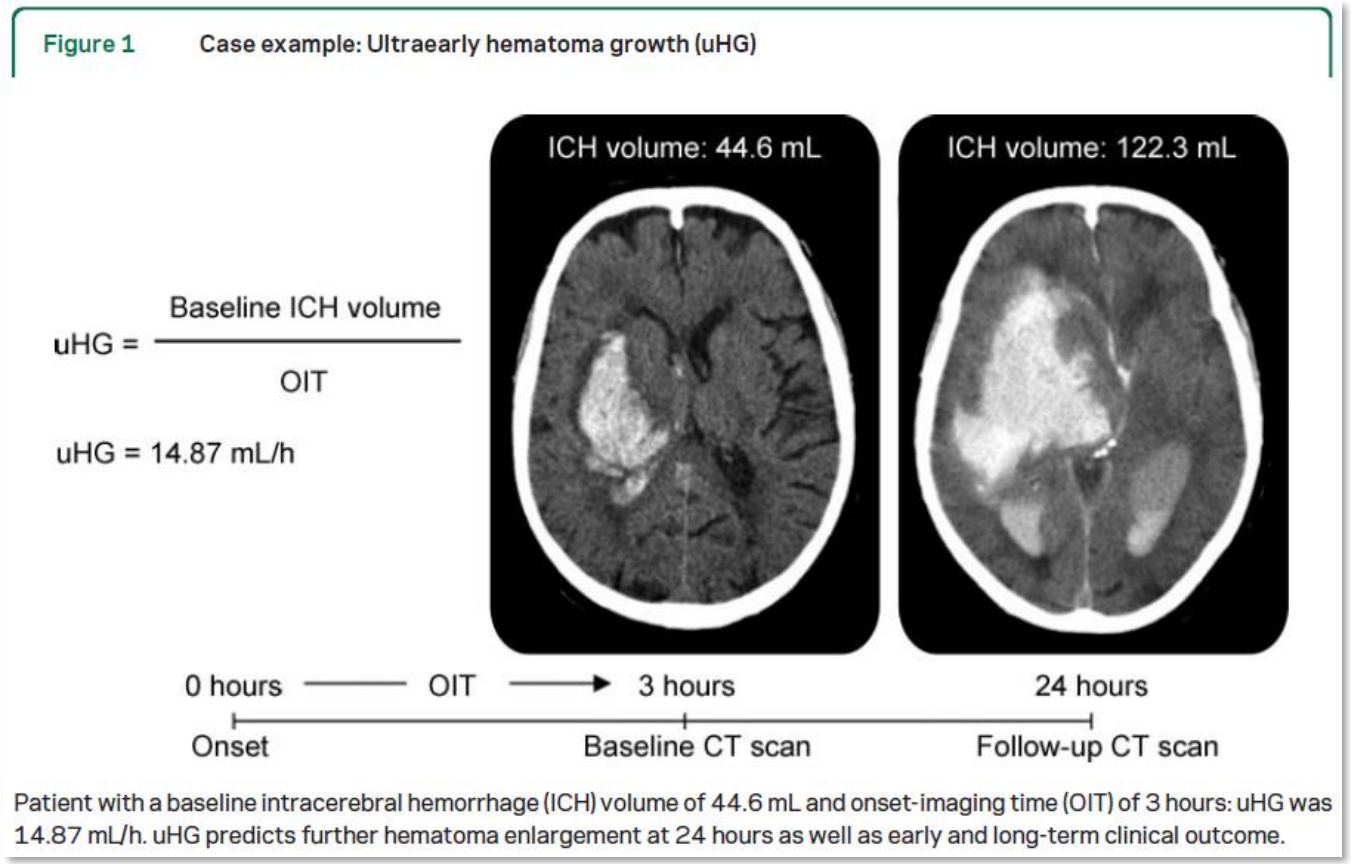
The impact of ICH volume on expansion may vary widely depending on the time from symptoms onset



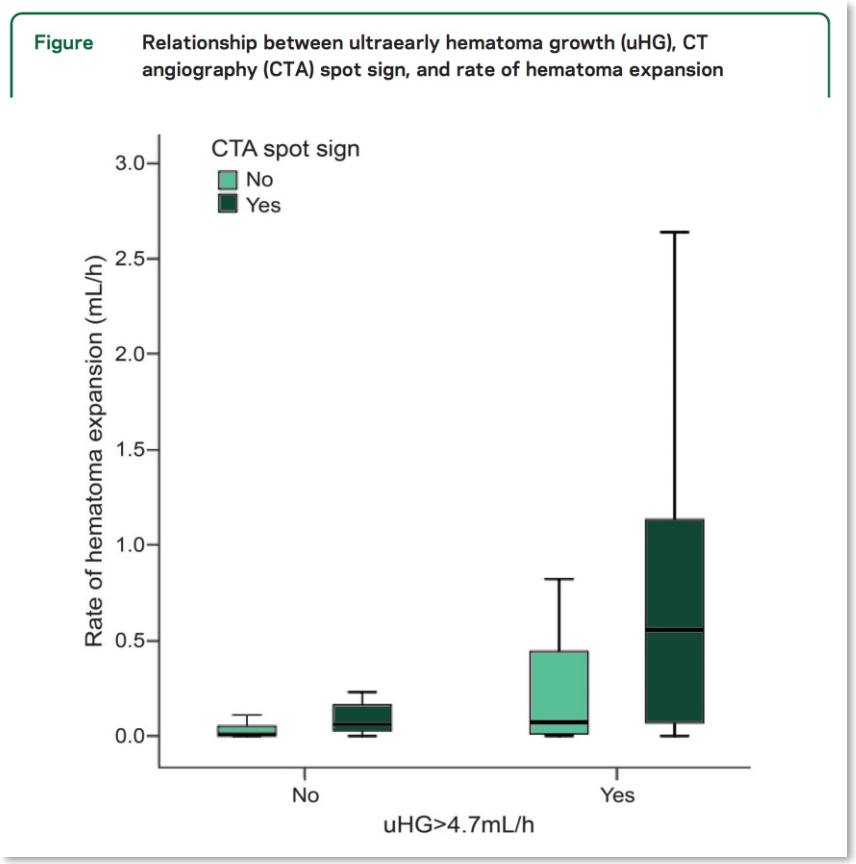
D. Rodriguez-Luna

Ultraearly hematoma growth (uHG)

uHG as the adjustment of ICH volume by the time from symptom onset



Rodriguez-Luna et al. *Neurology*. 2011; 77: 1599–1604

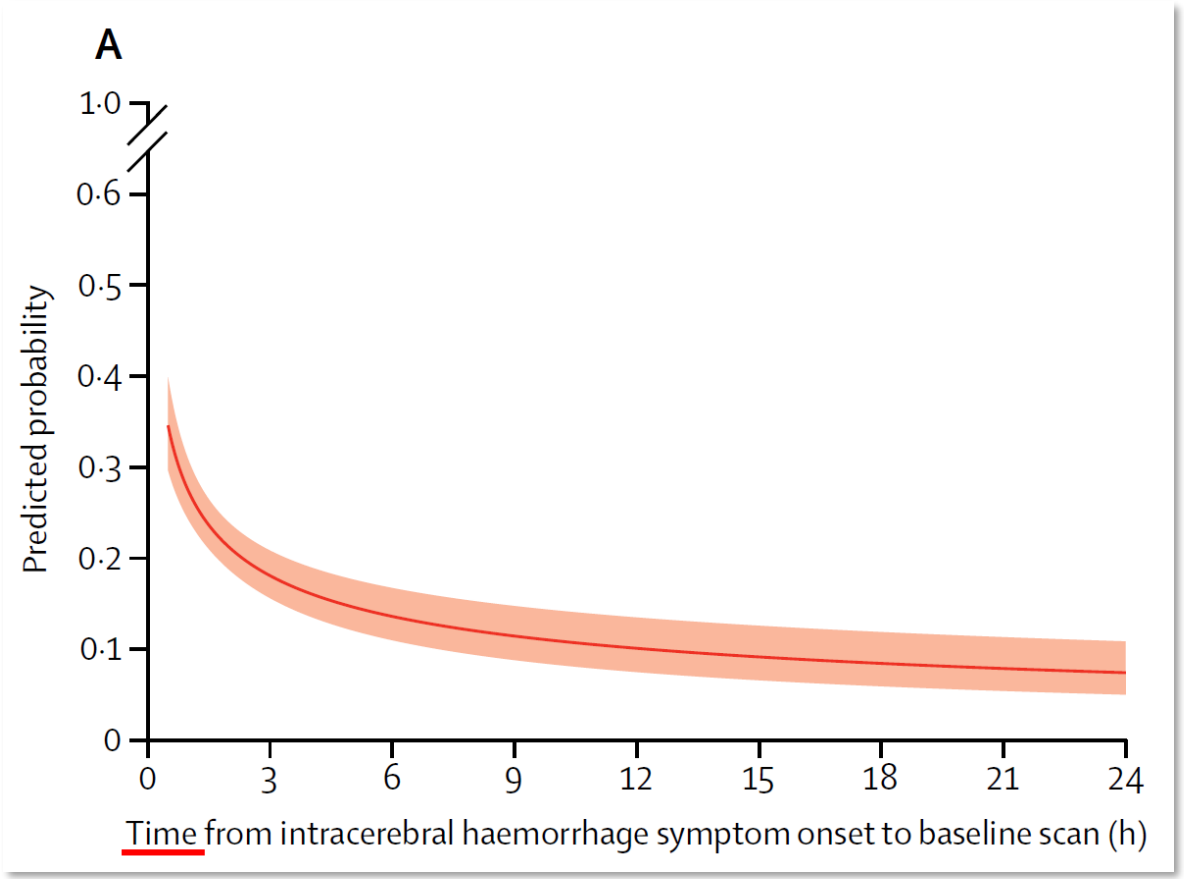


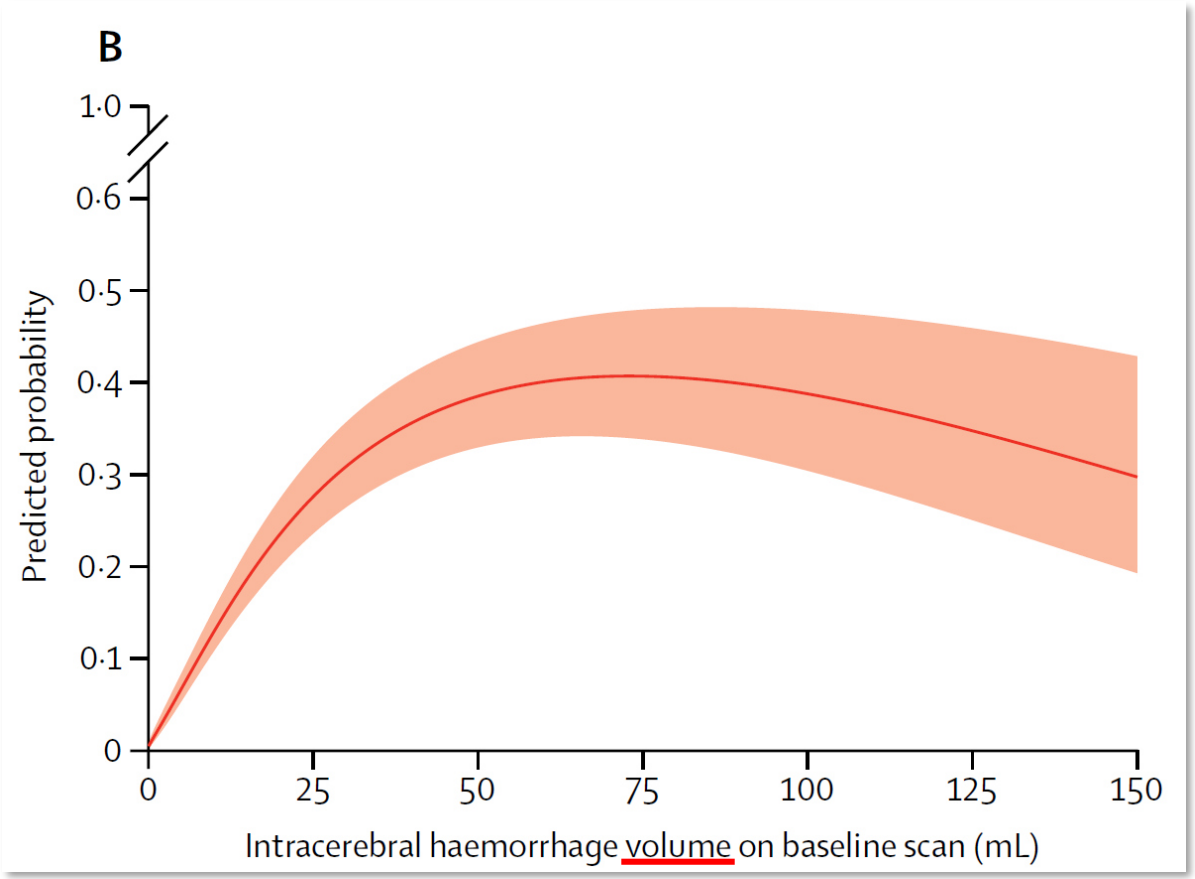
Rodriguez-Luna et al. *Neurology*. 2016; 87: 357–364

Represents the rate of expansion before hospital presentation

Timing of neuroimaging and ICH volume

Predicted probability of hematoma expansion





Salman et al. *Lancet Neurol*. 2018; 17: 885–894

Predictors of hematoma expansion

Four predictors

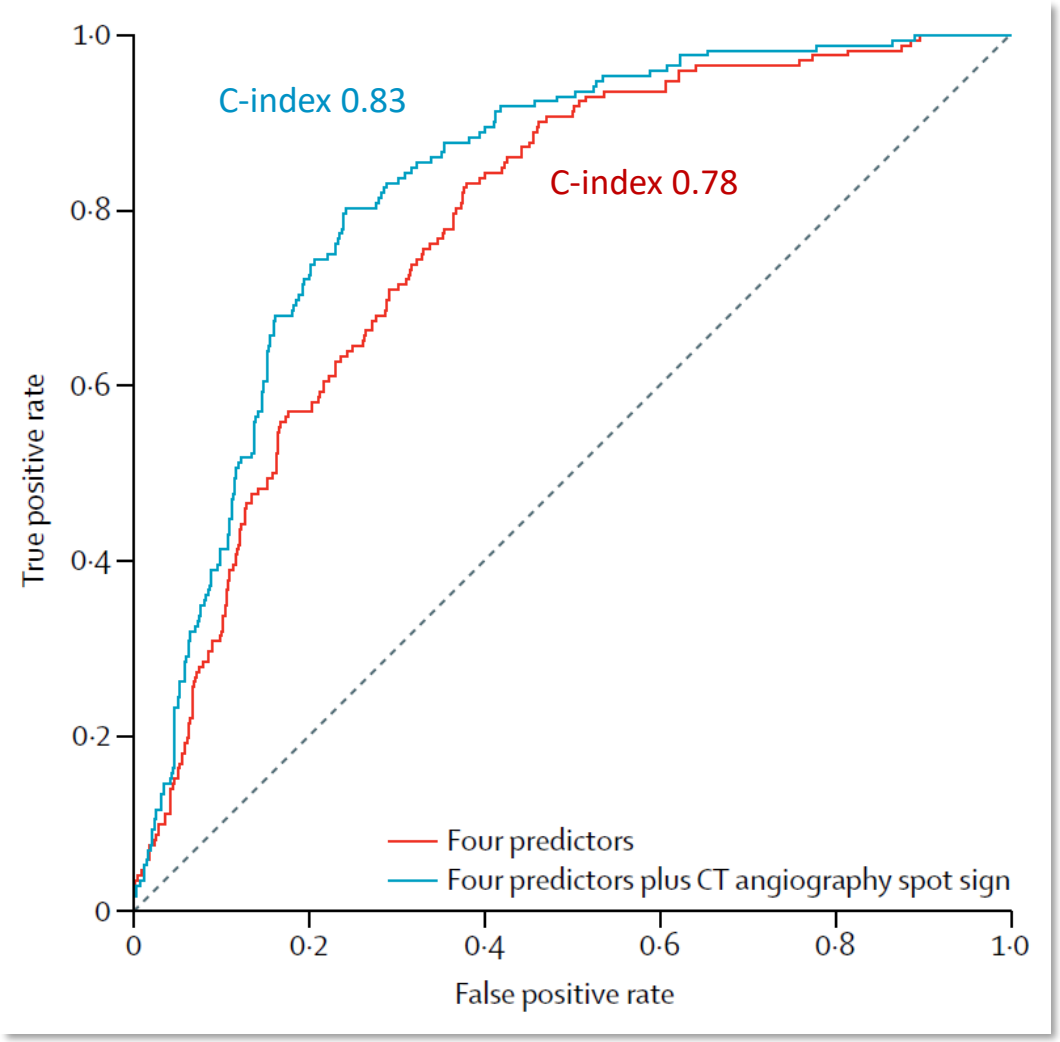
- Timing of neuroimaging
- ICH volume
- Antiplatelets
- Anticoagulants

Acceptable discrimination for expansion

Five predictors

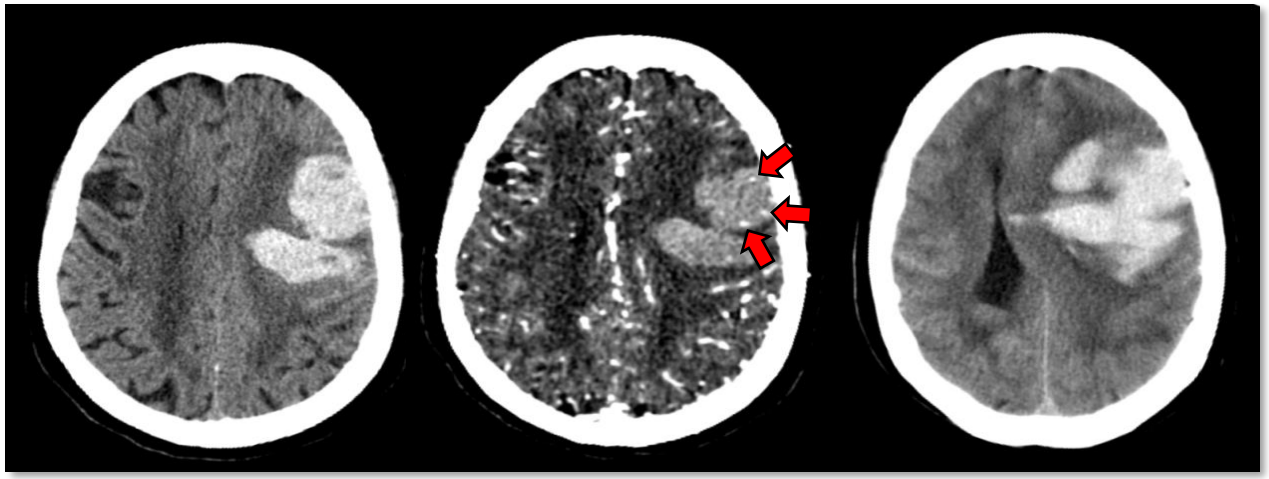
- + sCTA spot sign

Improved the C-index of the model



Salman et al. *Lancet Neurol*. 2018; 17: 885–894

CTA spot sign



A focus of **contrast enhancement** within hematoma visible on CTA source images

Validated in a multicentric study as a powerful predictor of hematoma expansion

Used in **some trials** to select patients for anti-expansion treatments

Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study

Andrew M Demchuk , Dar Dowlatshahi, David Rodriguez-Luna, Carlos A Molina, Yolanda Silva Blas, Imanuel Dzialowski, Adam Kobayashi, Jean-Martin Boulanger, Cheemun Lum, Gord Gubitz, Vasantha Padma, Jayanta Roy, Carlos S Kase, Jayme Kosior, Rohit Bhatia, Sarah Tymchuk, Suresh Subramaniam, David J Gladstone, Michael D Hill, Richard I Aviv, for the PREDICT/Sunnybrook ICH CTA study group

Lancet Neurol 2012; 11: 307–14

Summary

Background In patients with intracerebral haemorrhage (ICH), early haemorrhage expansion affects clinical outcome. Haemostatic treatment reduces haematoma expansion, but fails to improve clinical outcomes in many patients. Proper selection of patients at high risk for haematoma expansion seems crucial to improve outcomes. In this study, we aimed to prospectively validate the CT-angiography (CTA) spot sign for prediction of haematoma expansion.

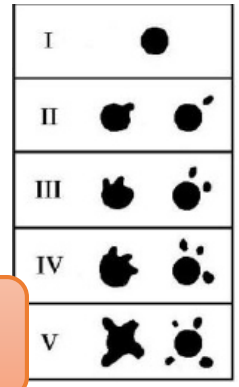
Methods PREDICT (predicting haematoma growth and outcome in intracerebral haemorrhage using contrast bolus CT) was a multicentre prospective observational cohort study. We recruited patients aged 18 years or older, with ICH smaller than 100 mL, and presenting at less than 6 h from symptom onset. Using two independent core laboratories, one neuroradiologist determined CTA spot-sign status, whereas another neurologist masked for clinical outcomes and imaging measured haematoma volumes by computerised planimetry. The primary outcome was haematoma expansion defined as absolute growth greater than 6 mL or a relative growth of more than 33% from initial CT to follow-up CT. We reported data using standard descriptive statistics stratified by the CTA spot sign. Mortality was assessed with Kaplan-Meier survival analysis.

Findings We enrolled 268 patients. Median time from symptom onset to baseline CT was 135 min (range 22–470), and time from onset to CTA was 159 min (32–475). 81 (30%) patients were spot-sign positive. The primary analysis included 228 patients, who had a follow-up CT before surgery or death. Median baseline ICH volume was 19·9 mL (1·5–80·9) in spot-sign-positive patients versus 10·0 mL (0·1–102·7) in spot-sign negative patients (p<0·001). Median ICH expansion was 8·6 mL (–9·3 to 121·7) for spot-sign positive patients and 0·4 mL (–11·7 to 98·3) for spot-negative patients (p<0·001). In those with haematoma expansion, the positive predictive value for the spot sign was 73%; the negative predictive value was 84%, sensitivity was 63%, and specificity was 90%. Median 3-month modified Rankin Scale (mRS) was 5 in CTA spot-sign-positive patients, and 3 in spot-sign-negative patients (p<0·001). Mortality at 3 months was 43·4% (23 of 53) in CTA spot-sign positive versus 19·6% (31 of 158) in CTA spot-sign-negative patients (HR 2·4, 95% CI 1·4–4·0, p=0·002).

Interpretation These findings confirm previous single-centre studies showing that the CTA spot sign is a predictor of haematoma expansion. The spot sign is recommended as an entry criterion for future trials of haemostatic therapy in patients with acute ICH.

D. Rodriguez-Luna

Non-contrast CT markers of expansion (apart from ICH volume)



Shape

Irregularity scale (Fujii et al.)

Irregular (Barras et al.)

Satellite sign (Shimoda et al.)

Island sign (Li et al.)

1994 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019

Swirl sign (Kim et al.)

Heterogeneous (Barras et al.)

Swirl sign (Selariu et al.)

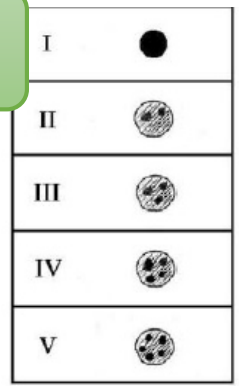
Blend sign (Li et al.)

Fluid level (Blacquerie et al.)

Black hole sign (Li et al.)

Hypodensities (Boulouis et al.)

Standardization (Morotti et al.)



Density

D. Rodriguez-Luna

Approaches to prevent hematoma expansion

Blood pressure control

INTERACT2, ATACH-II, INTERACT3 → **INTERACT4**

General hemostatic treatments

rFVIIa: phase IIb, FAST → SPOTLIGHT&STOP-IT → **FASTEST**

Tranexamic acid: CRASH-2, TICH-2 → STOP-AUST, TRAIGE → **TICH-3**

Anticoagulation reversal

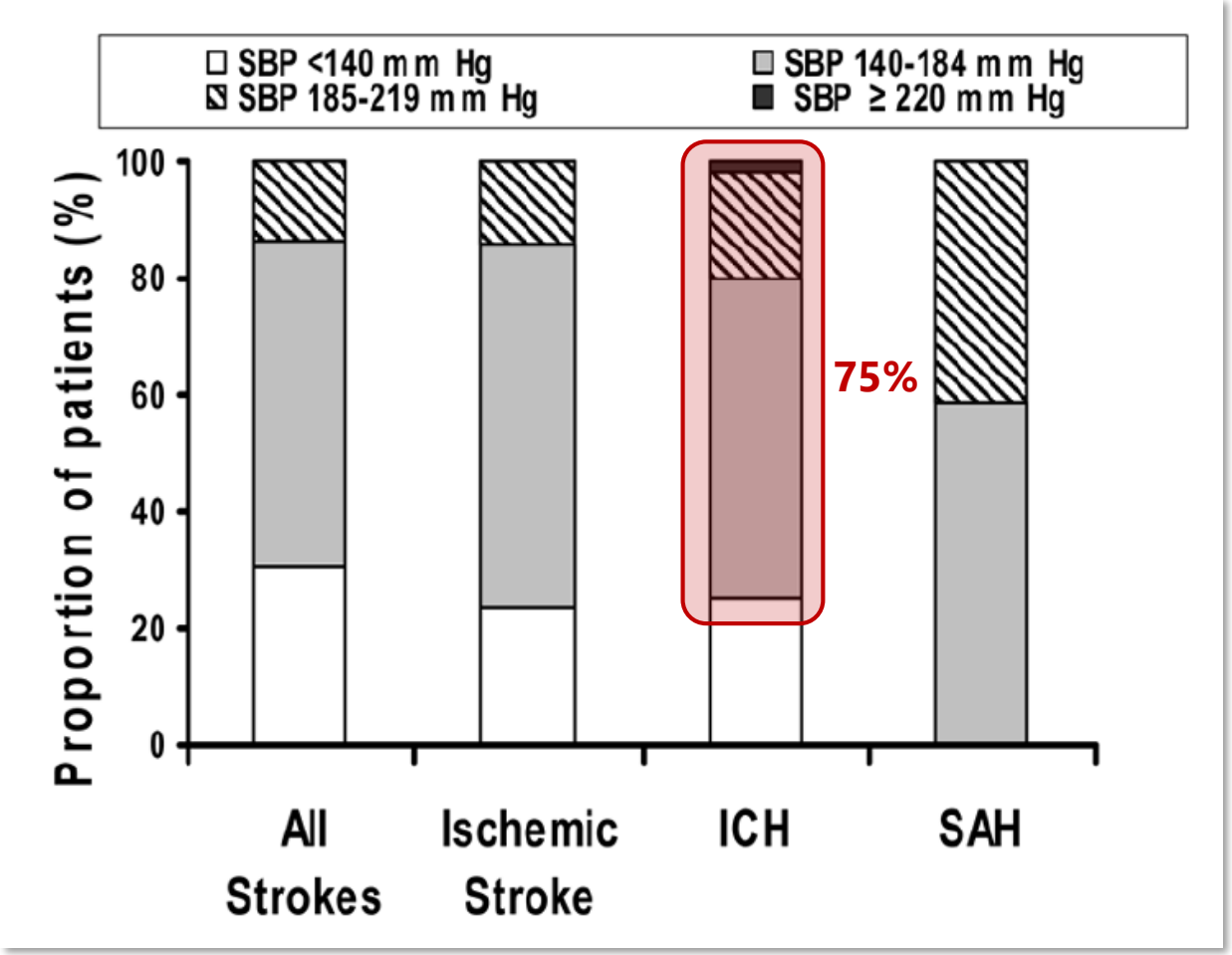
Vitamin K antagonists: INCH

Direct oral anticoagulants: RE-VERSE AD

ANNEXa-I

Blood Pressure Control

Elevation in BP in acute ICH



Qureshi et al. *Am J Emerg Med*. 2007; 25: 32–38

Elevation in BP and BP variability and outcome

Outcome	PICH Studies/Subjects	OR (95% CI)	P
Death			
SBP	3/244	3.55 (1.80, 7.00)	<0.01*
MABP	3/354	2.26 (1.40, 3.66)	<0.01*
DBP	2/162	1.74 (0.88, 3.46)	0.11
Death/disability			
SBP	1/87	2.69 (1.13, 6.40)	0.03*
MABP	2/199	2.90 (1.57, 5.36)	<0.01*
DBP	1/87	4.68 (1.87, 11.70)	<0.01*
Death/deterioration			
SBP	1/40	5.57 (1.42, 21.86)	0.01*

*$P<0.05$.

Willmot al. *Hypertension*. 2004; 43: 18–24

Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage

D. Rodriguez-Luna[a], S. Piñeiro[a], M. Rubiera[a], M. Ribo[a], P. Coscojuela[b], J. Pagola[a], A. Flores[a], M. Muchada[a], B. Ibarra[b], P. Meler[a], E. Sanjuan[a], M. Hernandez-Guillamon[a], J. Alvarez-Sabin[a], J. Montaner[a] and C. A. Molina[a]

[a]*Stroke Unit, Department of Neurology, Vall d'Hebron University Hospital, Vall d'Hebron Research Institute, Departament de Medicina, Universitat Autonoma de Barcelona, Barcelona; and* [b]*Department of Neuroradiology, Vall d'Hebron University Hospital, Barcelona, Spain*

European Journal of Neurology 2013, **20:** 1277–1283

Keywords:
blood pressure, hematoma growth, intracerebral hemorrhage, spot sign

Received 1 February 2013
Accepted 25 March 2013

Background and purpose: An association between high blood pressure (BP) in acute intracerebral hemorrhage (ICH) and hematoma growth (HG) has not been clearly demonstrated. Therefore, the impact of BP changes and course on HG and clinical outcome in patients with acute ICH was determined.

Methods: In total, 117 consecutive patients with acute (<6 h) supratentorial ICH underwent baseline and 24-h CT scans, CT angiography for the detection of the spot sign and non-invasive BP monitoring at 15-min intervals over the first 24 h. Maximum and minimum BP, maximum BP increase and drop from baseline, and BP variability values from systolic BP (SBP), diastolic BP and mean arterial pressure (MAP) were calculated. SBP and MAP loads were defined as the proportion of readings >180 and >130 mmHg, respectively. HG (>33% or >6 ml), early neurological deterioration (END) and 3-month mortality were recorded.

Results: Baseline BP variables were unrelated to either HG or clinical outcome. Conversely, SBP 180-load independently predicted HG (odds ratio 1.05, 95% CI 1.010–1.097, $P = 0.016$), whilst both SBP 180-load (odds ratio 1.04, 95% CI 1.001–1.076, $P = 0.042$) and SBP variability (odds ratio 1.2, 95% CI 1.047–1.380, $P = 0.009$) independently predicted END. Although none of the BP monitoring variables was associated with HG in the spot-sign-positive group, higher maximum BP increases from baseline and higher SBP and MAP loads were significantly related to HG in the spot-sign-negative group.

Conclusions: In patients with acute supratentorial ICH, SBP 180-load independently predicts HG, whilst both SBP 180-load and SBP variability predict END.

Rodriguez-Luna et al. *Eur J Neurol*. 2013; 20: 1277–1283

Elevation in BP and BP variability and outcome

Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial

*Lisa Manning, *Yoichiro Hirakawa, Hisatomi Arima, Xia Wang, John Chalmers, Jiguang Wang, Richard Lindley, Emma Heeley, Candice Delcourt, Bruce Neal, Pablo Lavados, Stephen M Davis, Christophe Tzourio, Yining Huang, Christian Stapf, Mark Woodward, Peter M Rothwell, Thompson G Robinson, Craig S Anderson, for the INTERACT2 investigators†

Summary

Background High blood pressure is a prognostic factor for acute stroke, but blood pressure variability might also independently predict outcome. We assessed the prognostic value of blood pressure variability in participants of INTERACT2, an open-label randomised controlled trial (ClinicalTrials.gov number NCT00716079).

Methods INTERACT2 enrolled 2839 adults with spontaneous intracerebral haemorrhage (ICH) and high systolic blood pressure (150–220 mm Hg) without a definite indication or contraindication to early intensive treatment to reduce blood pressure. Participants were randomly assigned to intensive treatment (target systolic blood pressure <140 mm Hg within 1 h using locally available intravenous drugs) or guideline-recommended treatment (target systolic blood pressure <180 mm Hg) within 6 h of onset of ICH. The primary outcome was death or major disability at 90 days (modified Rankin Scale score ≥3) and the secondary outcome was an ordinal shift in modified Rankin Scale scores at 90 days, assessed by investigators masked to treatment allocation. Blood pressure variability was defined according to standard criteria: five measurements were taken in the first 24 h (hyperacute phase) and 12 over days 2–7 (acute phase). We estimated associations between blood pressure variability and outcomes with logistic and proportional odds regression models. The key parameter for blood pressure variability was standard deviation (SD) of systolic blood pressure, categorised into quintiles.

Findings We studied 2645 (93·2%) participants in the hyperacute phase and 2347 (82·7%) in the acute phase. In both treatment cohorts combined, SD of systolic blood pressure had a significant linear association with the primary outcome for both the hyperacute phase (highest quintile adjusted OR 1·41, 95% CI 1·05–1·90; p_{trend}=0·0167) and the acute phase (highest quintile adjusted OR 1·57, 95% CI 1·14–2·17; p_{trend}=0·0124). The strongest predictors of outcome were maximum systolic blood pressure in the hyperacute phase and SD of systolic blood pressure in the acute phase. Associations were similar for the secondary outcome (for the hyperacute phase, highest quintile adjusted OR 1·43, 95% CI 1·14–1·80; p_{trend}=0·0014; for the acute phase OR 1·46, 95% CI 1·13–1·88; p_{trend}=0·0044).

Interpretation Systolic blood pressure variability seems to predict a poor outcome in patients with acute intracerebral haemorrhage. The benefits of early treatment to reduce systolic blood pressure to 140 mm Hg might be enhanced by smooth and sustained control, and particularly by avoiding peaks in systolic blood pressure.

Manning al. *Lancet Neurol*. 2014; 13: 364–373

Increased Blood Pressure Variability Contributes to Worse Outcome After Intracerebral Hemorrhage

An Analysis of ATACH-2

Adam de Havenon, MD; Jennifer J. Majersik, MD, MS; Gregory Stoddard, MPH, MBA; Ka-Ho Wong, BS; J. Scott McNally, MD, PhD; A. Gordon Smith, MD; Natalia S. Rost, MD, MPH; David L. Tirschwell, MD, MSc

Background and Purpose—Increased systolic blood pressure variability (BPV) is associated with worse outcome after acute ischemic stroke and may also have a negative impact after intracerebral hemorrhage. We sought to determine whether increased BPV was detrimental in the ATACH-2 (Antihypertensive Treatment of Acute Cerebral Hemorrhage II) trial.

Methods—The primary outcome of our study was a 3-month follow-up modified Rankin Scale of 3 to 6, and the secondary outcome was a utility-weighted modified Rankin Scale. We calculated blood pressure mean and variability using systolic blood pressure from the acute period (2–24 hours postrandomization) and subacute period (days 2, 3, and 7).

Results—The acute period included 913 patients and the subacute included 877. For 5 different statistical measures of systolic BPV, there was a consistent association between increased BPV and worse neurological outcome in both the acute and subacute periods. This association was not found for systolic blood pressure mean.

Conclusions—In this secondary analysis of ATACH-2, we show that increased systolic BPV is associated with worse long-term neurological outcome. Additional research is needed to find techniques that allow early identification of patients with an expected elevation of BPV and to study pharmacological or protocol-based approaches to minimize BPV. **(*Stroke*. 2018;49:1981-1984. DOI: 10.1161/STROKEAHA.118.022133.)**

It is not only important to **maintain low BP**, but also to **keep it stable**

D. Rodriguez-Luna

Intensive BP lowering and functional outcome, early RCT

Inconsistent results

INTERACT2

Variable	Intensive Blood-Pressure Lowering (N=1399)	Guideline-Recommended Blood-Pressure Lowering (N=1430)	Odds Ratio (95% CI)	P Value
Primary outcome: death or major disability — no./total no. (%)†	719/1382 (52.0)	785/1412 (55.6)	0.87 (0.75–1.01)	0.06
Secondary outcomes				
Score on the modified Rankin scale — no./total no. (%)‡			0.87 (0.77–1.00)	0.04
0: No symptoms at all	112/1382 (8.1)	107/1412 (7.6)		
1: No substantive disability despite symptoms	292/1382 (21.1)	254/1412 (18.0)		
2: Slight disability	259/1382 (18.7)	266/1412 (18.8)		
3: Moderate disability requiring some help	220/1382 (15.9)	234/1412 (16.6)		
4: Moderate–severe disability requiring assistance with daily living	250/1382 (18.1)	268/1412 (19.0)		
5: Severe disability, bed-bound and incontinent	83/1382 (6.0)	113/1412 (8.0)		
6: Death by 90 days	166/1382 (12.0)	170/1412 (12.0)		
Death — no./total no. (%)	166/1394 (11.9)	170/1421 (12.0)	0.99 (0.79–1.25)	0.96
Health-related quality of life§				
Problems with mobility — no./total no. (%)	767/1203 (63.8)	821/1231 (66.7)	0.88 (0.74–1.04)	0.13
Problems with self-care — no./total no. (%)	563/1202 (46.8)	635/1230 (51.6)	0.83 (0.70–0.97)	0.02
Problems with usual activities — no./total no. (%)	731/1203 (60.8)	814/1231 (66.1)	0.79 (0.67–0.94)	0.006
Problems with pain or discomfort — no./total no. (%)	477/1197 (39.8)	552/1227 (45.0)	0.81 (0.69–0.95)	0.01
Problems with anxiety or depression — no./total no. (%)	406/1192 (34.1)	463/1220 (38.0)	0.84 (0.72–1.00)	0.05
Overall health utility score	0.60±0.39	0.55±0.40		0.002

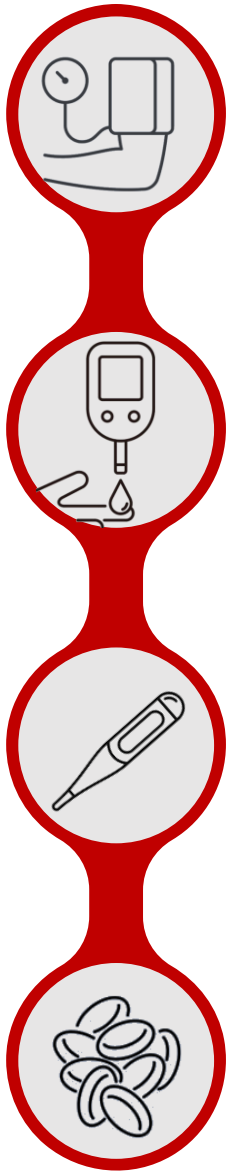
Anderson et al. *NEJM.* 2013; 368: 2355–2365

ATACH-II Antihypertensive Treatment of Cerebral Hemorrhage

	Intensive Treatment (N=500)	Standard Treatment (N=500)	Adjusted Analysis†	
			Relative Risk or Beta Estimate (95% CI)	P Value
Primary outcome: death or disability — no./total no. (%)‡	186/481 (38.7)	181/480 (37.7)	1.04 (0.85 to 1.27)	0.72
Hematoma expansion — no./total no. (%)§	85/450 (18.9)	104/426 (24.4)	0.78 (0.58 to 1.03)	0.08
Neurologic deterioration within 24 hr — no. (%)¶	55 (11.0)	40 (8.0)	1.39 (0.92 to 2.09)	0.11
Treatment-related serious adverse event within 72 hr — no. (%)‖	8 (1.6)	6 (1.2)	1.37 (0.47 to 3.95)	0.56
Any serious adverse event within 3 mo — no. (%)	128 (25.6)	100 (20.0)	1.30 (1.00 to 1.69)	0.05
Hypotension within 72 hr — no. (%)	6 (1.2)	3 (0.6)	1.96 (0.49 to 7.87)	0.34
Death — no. (%)	33 (6.6)	34 (6.8)	0.99 (0.61 to 1.60)	0.97
EQ-5D utility index score**††			−0.02 (−0.05 to 0.02)	0.29
Median	0.7	0.7		
Range	−0.1 to 1.0	0 to 1.0		
EQ-5D visual-analogue scale score**‡‡			−1.32 (−5.25 to 2.60)	0.51
Median	62.5	70		
Range	0 to 100	0 to 100		

Qureshi et al. *NEJM.* 2016; 375: 1033–1043

Intensive BP lowering and functional outcome, care bundle

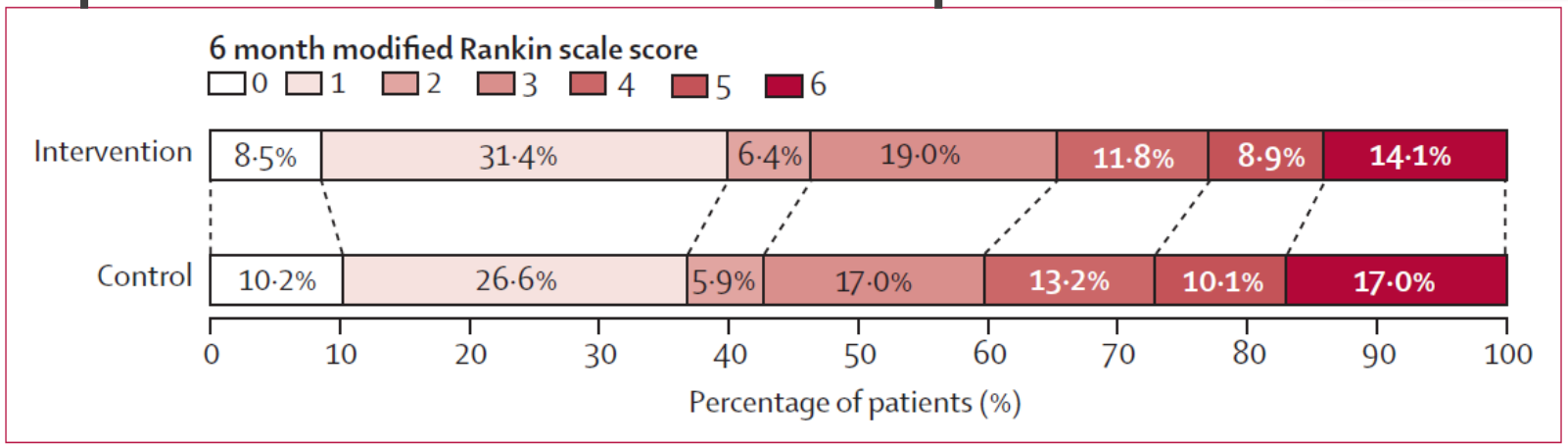


Rather than testing intensive BP lowering as a single intervention

↓

Different measures were combined in a care bundle, including intensive BP lowering

Intensive BP lowering, as part of a care bundle protocol, leads to improved functional outcomes in patients with acute ICH



Ma et al. *Lancet*. 2023; 402: 27–40

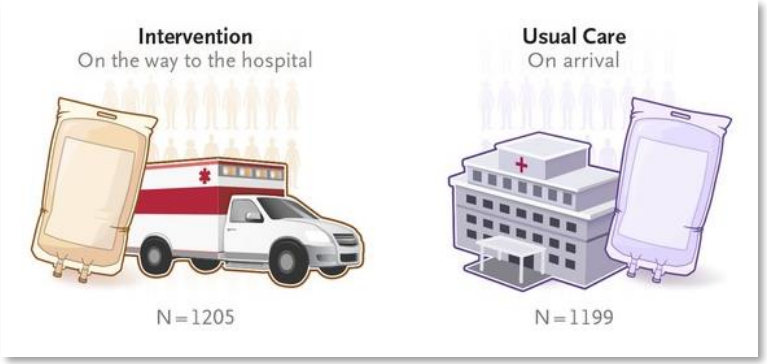
Intensive BP lowering and functional outcome, influence of time

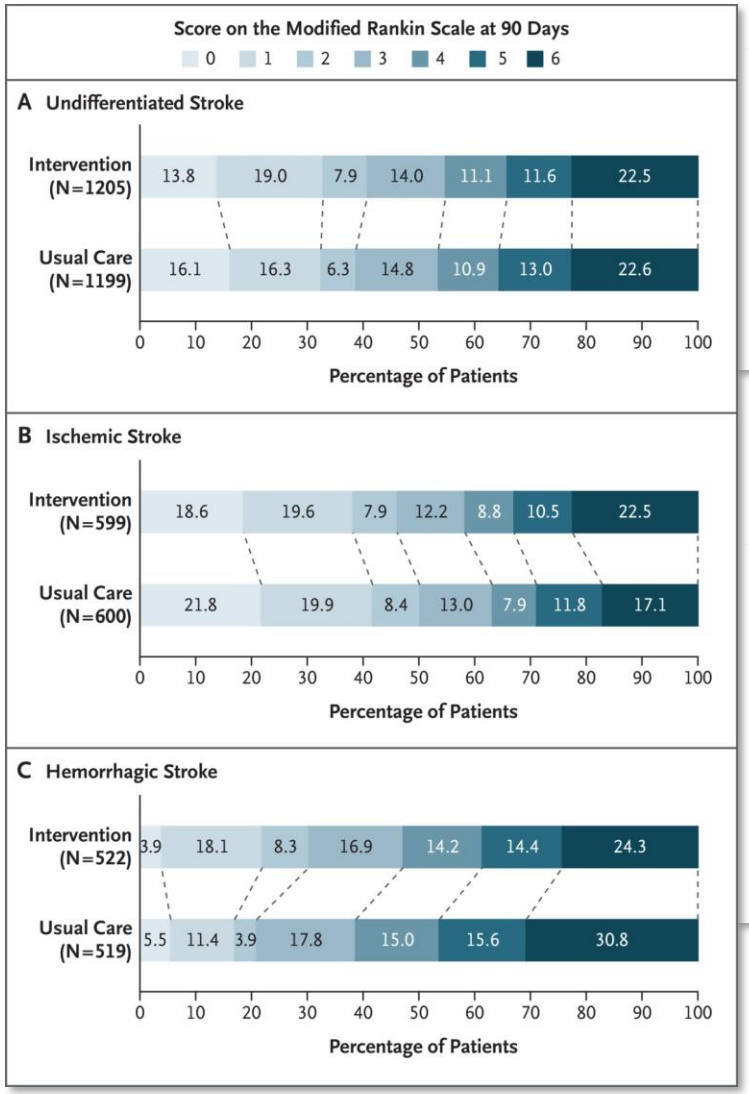
Intensive Ambulance-Delivered Blood-Pressure Reduction in Hyperacute Stroke

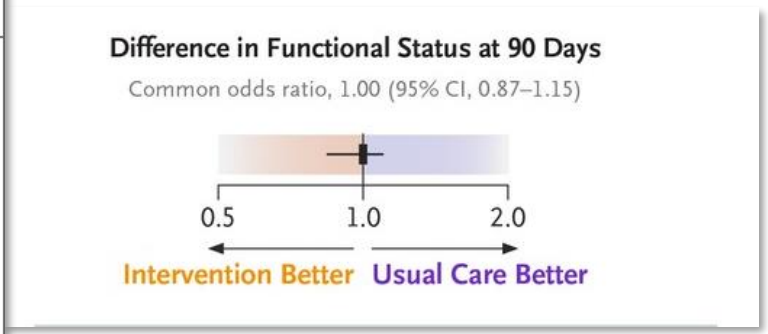
G. Li, Y. Lin, J. Yang, C.S. Anderson, C. Chen, F. Liu, L. Billot, Q. Li, X. Chen, X. Liu, X. Ren, C. Zhang, P. Xu, L. Wu, F. Wang, D. Qiu, M. Jiang, Y. Peng, C. Li, Y. Huang, X. Zhao, J. Liang, Y. Wang, X. Wu, Xiaoyun Xu, G. Chen, D. Huang, Y. Zhang, L. Zuo, G. Ma, Y. Yang, J. Hao, Xiahong Xu, X. Xiong, Y. Tang, Y. Guo, J. Yu, S. Li, S. He, F. Mao, Q. Tan, S. Tan, N. Yu, R. Xu, M. Sun, B. Li, J. Guo, L. Liu, H. Liu, M. Ouyang, L. Si, H. Arima, P.M. Bath, G.A. Ford, T. Robinson, E.C. Sandset, J.L. Saver, N. Sprigg, H.B. van der Worp, and L. Song, for the INTERACT4 investigators*

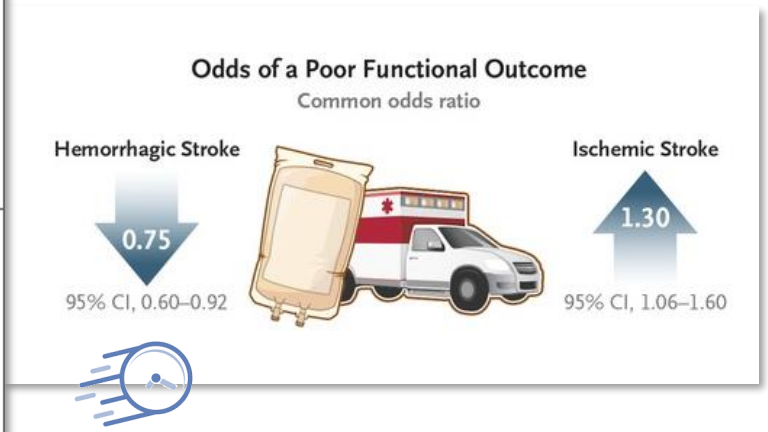
NEJM. 2024; 390: 1862–1872

Pt. with suspected stroke & SBP >150 mmHg



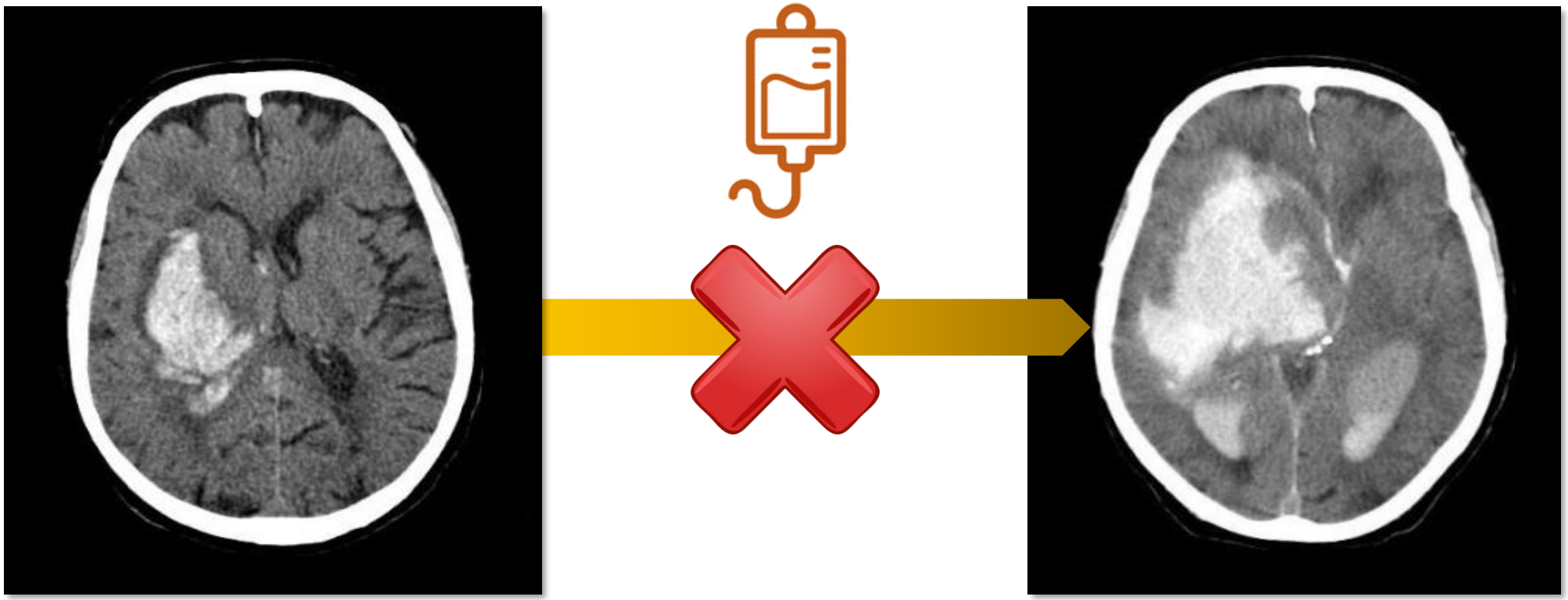






Intensive BP lowering, what is the mechanism of action?

The benefit of intensive BP lowering is believed to be driven by the attenuation of expansion



Intensive BP lowering and ICH expansion

RCT failed to show an impact of intensive BP lowering treatment on expansion

	Guideline (n=172)	Intensive (n=174)	Difference (95% CI)*	p
Haematoma				
Mean baseline volume (mL)	12·7 (11·6)	14·2 (14·5)	..	..
Mean volume at 24 h (mL)	15·4 (14·7)	15·2 (17·5)	..	..
Proportional increase (%)				
Mean (95% CI)	36·3% (15·8 to 56·8%)	13·7% (5·9 to 21·5%)	22·6% (0·6 to 44·5%)	0·04
Adjusted median (95% CI)†	16·2% (8·8 to 24·1%)	6·2% (−0·7 to 13·4%)	10·0% (0·0 to 20·5%)	0·06
Absolute increase (mL)				
Mean (95% CI)	2·7 (1·4 to 4·0)	0·9 (−0·9 to 2·7)	1·7 (−0·5 to 4·0)	0·12
Adjusted mean (95% CI)	2·6 (1·1 to 4·2)	0·9 (−0·6 to 2·5)	1·7 (−0·5 to 3·9)	0·13
Substantial growth‡	40 (23%)	26 (15%)	8% (−1·0 to 17·0%)§	0·05

Anderson et al. *Lancet Neurol*. 2008; 7: 391–399

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

	Blood Pressure Lowering				Absolute (mL) or proportional (%) decrease in intensive group	
	Intensive Group (N = 491)		Guideline Group (N = 473)			
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.

Anderson et al. *NEJM.* 2013; 368: 2355–2365

Treat. initiation: 4h
33% target ≤60 min
35% follow-up CT

Intensive BP lowering and ICH expansion

Meta-analyses have shown a greater reduction of expansion with intensive BP management

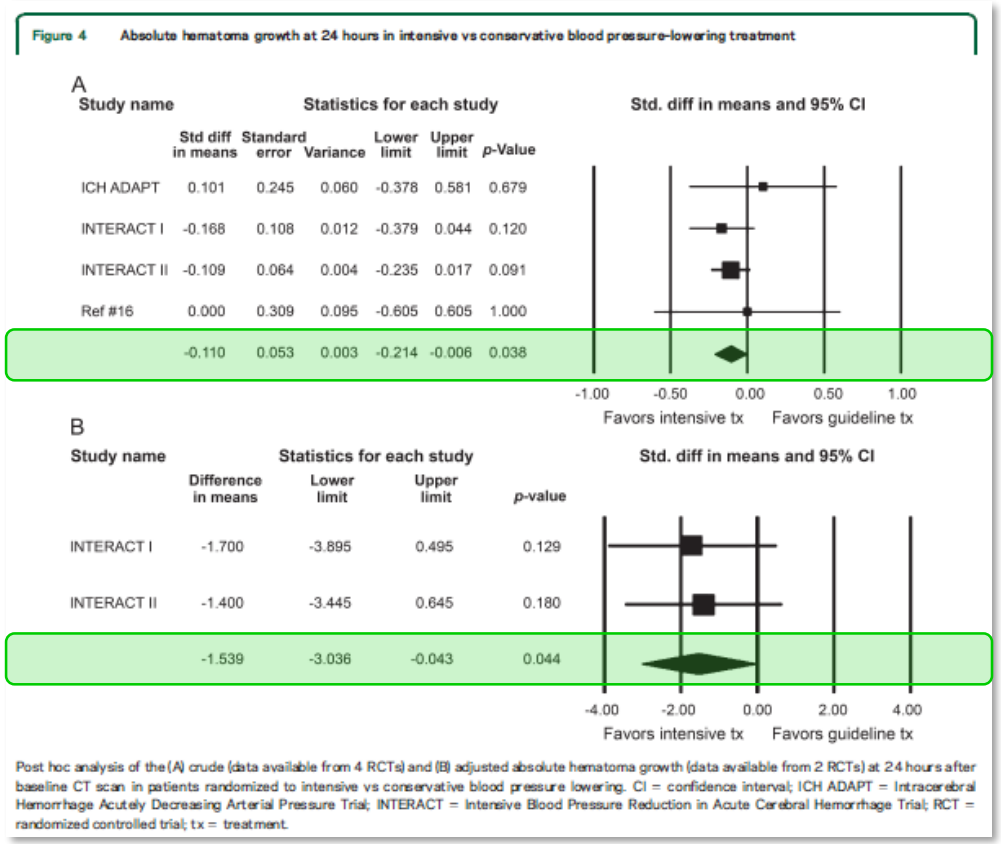


Figure 4 Absolute hematoma growth at 24 hours in intensive vs conservative blood pressure-lowering treatment

A

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	p-Value
ICH ADAPT	0.101	0.245	0.060	-0.378	0.581	0.679
INTERACT I	-0.168	0.108	0.012	-0.379	0.044	0.120
INTERACT II	-0.109	0.064	0.004	-0.235	0.017	0.091
Ref #16	0.000	0.309	0.095	-0.605	0.605	1.000
	-0.110	0.053	0.003	-0.214	-0.006	0.038

Statistics for each study — Std. diff in means and 95% CI

-1.00 -0.50 0.00 0.50 1.00

Favors intensive tx Favors guideline tx

B

Study name	Difference in means	Lower limit	Upper limit	p-value
INTERACT I	-1.700	-3.895	0.495	0.129
INTERACT II	-1.400	-3.445	0.645	0.180
	-1.539	-3.036	-0.043	0.044

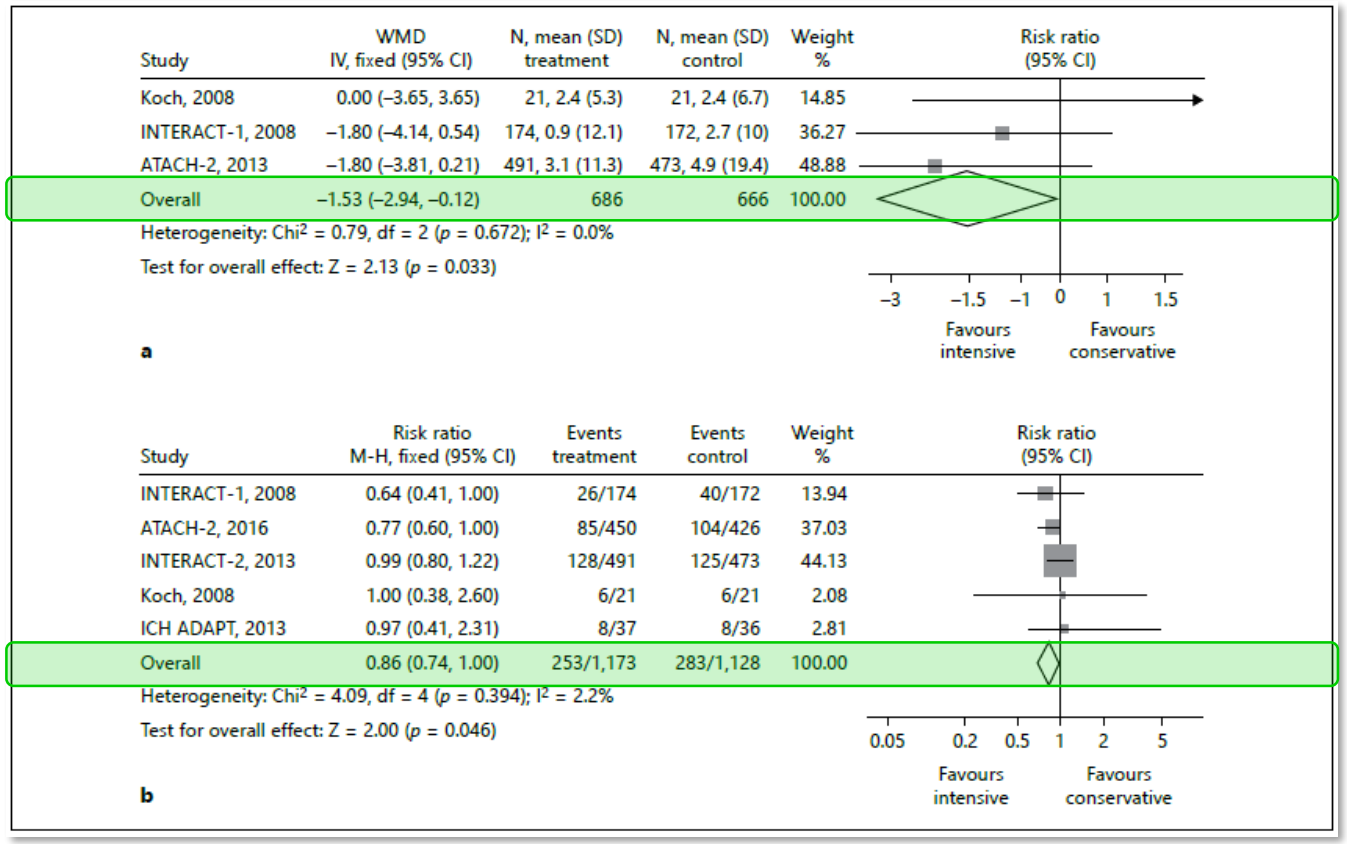
Statistics for each study — Std. diff in means and 95% CI

-4.00 -2.00 0.00 2.00 4.00

Favors intensive tx Favors guideline tx

Post hoc analysis of the (A) crude (data available from 4 RCTs) and (B) adjusted absolute hematoma growth (data available from 2 RCTs) at 24 hours after baseline CT scan in patients randomized to intensive vs conservative blood pressure lowering. CI = confidence interval; ICH ADAPT = Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial; INTERACT = Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; RCT = randomized controlled trial; tx = treatment.

Tsivgoulis et al. *Neurology*. 2014; 83: 1523–1529



Study	WMD IV, fixed (95% CI)	N, mean (SD) treatment	N, mean (SD) control	Weight %
Koch, 2008	0.00 (–3.65, 3.65)	21, 2.4 (5.3)	21, 2.4 (6.7)	14.85
INTERACT-1, 2008	–1.80 (–4.14, 0.54)	174, 0.9 (12.1)	172, 2.7 (10)	36.27
ATACH-2, 2013	–1.80 (–3.81, 0.21)	491, 3.1 (11.3)	473, 4.9 (19.4)	48.88
Overall	–1.53 (–2.94, –0.12)	686	666	100.00

Heterogeneity: $Chi^2 = 0.79$, df = 2 ($p = 0.672$); $I^2 = 0.0\%$

Test for overall effect: Z = 2.13 ($p = 0.033$)

Risk ratio (95% CI)

–3 –1.5 –1 0 1 1.5

Favours intensive Favours conservative

a

Study	Risk ratio M-H, fixed (95% CI)	Events treatment	Events control	Weight %
INTERACT-1, 2008	0.64 (0.41, 1.00)	26/174	40/172	13.94
ATACH-2, 2016	0.77 (0.60, 1.00)	85/450	104/426	37.03
INTERACT-2, 2013	0.99 (0.80, 1.22)	128/491	125/473	44.13
Koch, 2008	1.00 (0.38, 2.60)	6/21	6/21	2.08
ICH ADAPT, 2013	0.97 (0.41, 2.31)	8/37	8/36	2.81
Overall	0.86 (0.74, 1.00)	253/1,173	283/1,128	100.00

Heterogeneity: $Chi^2 = 4.09$, df = 4 ($p = 0.394$); $I^2 = 2.2\%$

Test for overall effect: Z = 2.00 ($p = 0.046$)

Risk ratio (95% CI)

0.05 0.2 0.5 1 2 5

Favours intensive Favours conservative

b

Lattanzi et al. *Cerebrovasc Dis*. 2017; 43: 207–213

Intensive BP lowering and ICH expansion. Influence of time

Post-hoc analyses

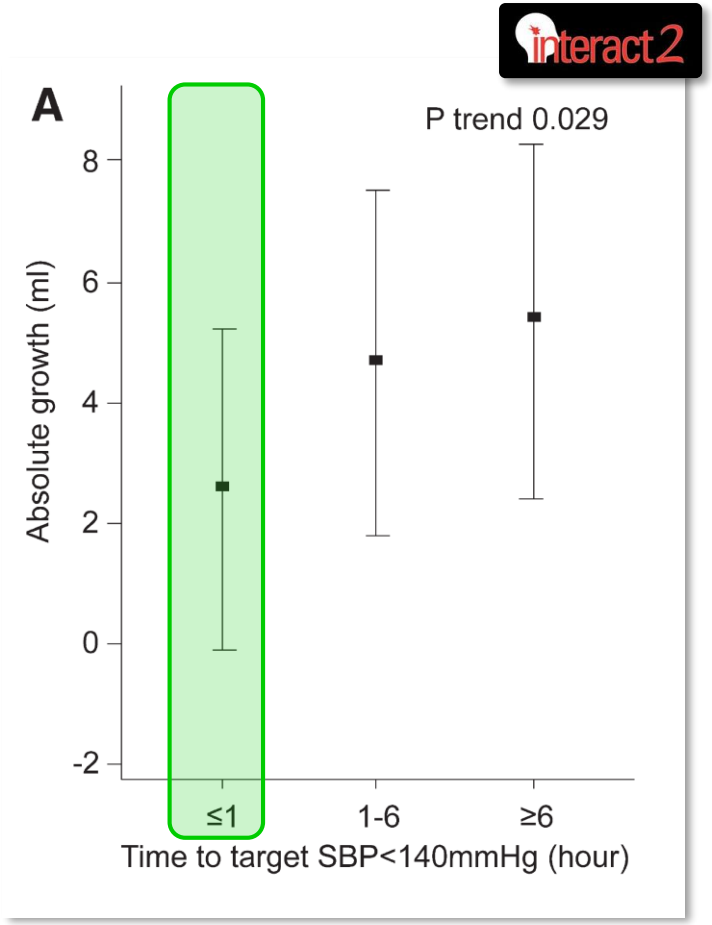
Early initiation of antihypertensive treatment

ATACH-II Antihypertensive Treatment of Cerebral Hemorrhage

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

Early achievement of the BP target



D. Rodriguez-Luna

Intensive BP lowering and ICH expansion. Influence of time

Effects of Achieving Rapid, Intensive, and Sustained Blood Pressure Reduction in Intracerebral Hemorrhage Expansion and Functional Outcome

David Rodriguez-Luna, MD, PhD, Olalla Pancorbo, RN, MSc, Laura Llull, MD, PhD, Yolanda Silva, MD, PhD, Luis Prats-Sanchez, MD, PhD, Marián Muchada, MD, PhD, Salvatore Rudilosso, MD, PhD, Mikel Terceño, MD, PhD, Anna Ramos-Pachón, MD, Mar Hernandez Guillamon, PhD, Pilar Coscojuela, MD, Jordi Blasco, MD, Santiago Perez-Hoyos, BSc, PhD, Angel Chamorro, MD, PhD, and Carlos A. Molina, MD, PhD, for the RAINS Study Group

Correspondence
Prof. Rodriguez-Luna
david.rodriguez@vallhebron.cat

Neurology® 2024;102:e209244. doi:10.1212/WNL.0000000000209244

Abstract

Background and Objectives

The time taken to achieve blood pressure (BP) control could be pivotal in the benefits of reducing BP in acute intracerebral hemorrhage (ICH). We aimed to assess the relationship between the rapid achievement and sustained maintenance of an intensive systolic BP (SBP) target with radiologic, clinical, and functional outcomes.

Methods

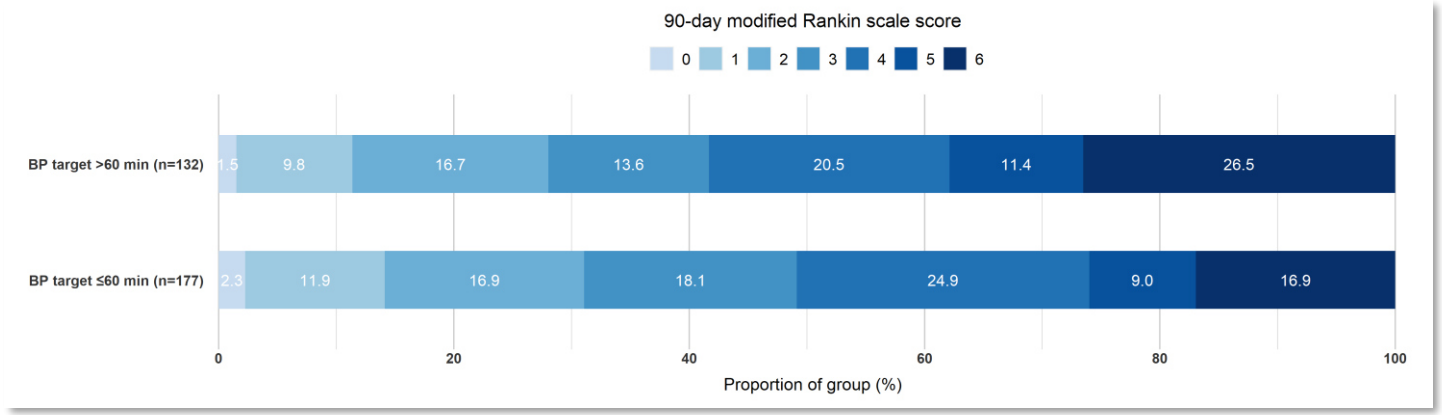
Rapid, Intensive, and Sustained BP lowering in Acute ICH (RAINS) was a multicenter, prospective, observational cohort study of adult patients with ICH <6 hours and SBP ≥150 mm Hg at 4 Comprehensive Stroke Centers during a 4.5-year period. Patients underwent baseline and 24-hour CT scans and 24-hour noninvasive BP monitoring. BP was managed under a rapid (target achievement ≤60 minutes), intensive (target SBP <140 mm Hg), and sustained (target stability for 24 hours) BP protocol. SBP target achievement ≤60 minutes and 24-hour SBP variability were recorded. Outcomes included hematoma expansion (>6 mL or >33%) at 24 hours (primary outcome), early neurologic deterioration (END, 24-hour increase in NIH Stroke Scale score ≥4), and 90-day ordinal modified Rankin scale (mRS) score. Analyses were adjusted by age, sex, anticoagulation, onset-to-imaging time, ICH volume, and intraventricular extension.

Results

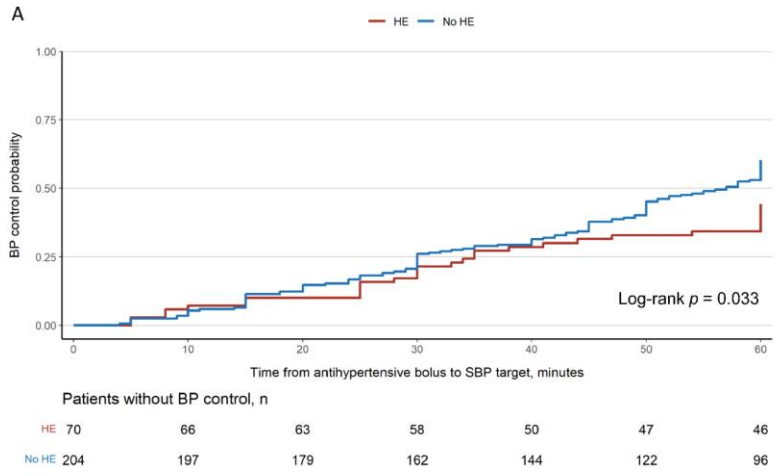
We included 312 patients (mean age 70.2 ± 13.3 years, 202 [64.7%] male). Hematoma expansion occurred in 70/274 (25.6%) patients, END in 58/291 (19.9%), and the median 90-day mRS score was 4 (interquartile range, 2–5). SBP target achievement ≤60 minutes (178/312 [57.1%]) associated with a lower risk of hematoma expansion (adjusted odds ratio [aOR] 0.43, 95% confidence interval [CI] 0.23–0.77), lower END rate (aOR 0.43, 95% CI 0.23–0.80), and lower 90-day mRS scores (aOR 0.48, 95% CI 0.32–0.74). The mean 24-hour SBP variability was 21.0 ± 7.6 mm Hg. Higher 24-hour SBP variability was not related to expansion (aOR 0.99, 95% CI 0.95–1.04) but associated with higher END rate (aOR 1.15, 95% CI 1.09–1.21) and 90-day mRS scores (aOR 1.06, 95% CI 1.04–1.10).

Discussion

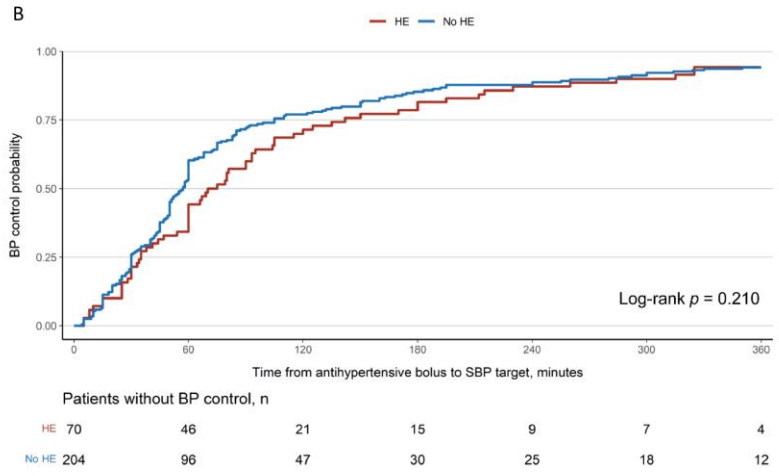
Among patients with acute ICH, achieving an intensive SBP target within 60 minutes was associated with lower hematoma expansion risk. Rapid SBP reduction and stable sustention within 24 hours were related to improved clinical and functional outcomes. These findings warrant the design of randomized clinical trials examining the impact of effectively achieving rapid, intensive, and sustained BP control on hematoma expansion.



Probability of BP control within **60 min** & Expansion



Probability of BP control within **6 hours** & Expansion



D. Rodriguez-Luna

Hemostatic agents

Hemostatic agents

Tested to prevent hematoma expansion in patients with acute ICH

- Recombinant activated factor VII (rFVIIa)
- Tranexamic acid (TXA)

Hemostatic treatments: tranexamic acid

TICH-2 (phase III)

n=2.325

ICH <8 hours

TXA vs. placebo

↓ Expansion

↓ 7d mortality

↓ SAEs

No ↑ thromboembolism

= 90d mRS

	Tranexamic acid (n=1161)	Placebo (n=1164)	Adjusted	
			Effect estimate (95% CI)	p value
Primary outcome, day 90				
Participants with mRS outcome	1152	1155	Ordinal OR 0·88 (0·76 to 1·03)	0·11
Sensitivity analysis, day 90				
mRS, unadjusted	..	..	Ordinal OR 1·00 (0·86 to 1·15)	0·97
mRS >3	814 (71%)	826 (72%)	Binary OR 0·82 (0·65 to 1·03)	0·08
Haematoma				
Change in volume from baseline to 24 h*, mL	3·72 (15·9)	4·90 (16·0)	MD −1·37 (−2·71 to −0·04)	0·0432
Participants with haematoma expansion†	265 (25%)	304 (29%)	Binary OR 0·80 (0·66 to 0·98)	0·0300
Day 7				
Death by day 7	101 (9%)	123 (11%)	Binary OR 0·73 (0·53 to 0·99)	0·0406
NIHSS day 7	10·13 (8·3)	10·29 (8·3)	MD −0·43 (−0·94 to 0·09)	0·10

Sprigg et al. *Lancet*. 2018; 391: 2107–2115

Hemostatic treatments: rFVIIa

FAST (phase III)

n=841

Treatment <4 hours

Single dose: Placebo, 20 or 80 μg rFVIIa/kg

Safety

Thromboembolic SAEs:

8% placebo, 9% 20 μg, 10% 80 μg (*p*=ns)

Arterial thromboembolic SAEs:

3% placebo, 4% 20 μg, 5% 80 μg (*p*=0.040)

Efficacy

Table 2. Hemorrhage Volumes at Baseline and Follow-up.*

Variable	rFVIIa, 20 μg/kg (N=276)	rFVIIa, 80 μg/kg (N=297)	Placebo (N=268)
Volume of intracerebral hemorrhage			
At baseline — ml	24±26	23±26	22±24
At 24 hr — ml	28±30	25±28	28±31
Estimated percent increase from baseline — mean (95% CI)	18 (13 to 24)	11 (6 to 17)	26 (20 to 32)
P value vs. placebo	0.09	<0.001	—
Estimated milliliters of increase from baseline — mean (95% CI)	4.9 (2.9 to 7.0)	3.7 (1.7 to 5.7)	7.5 (5.4 to 9.6)
P value vs. placebo	0.08	0.009	—

Table 3. Clinical Outcome and Thromboembolic Serious Adverse Events at 90 Days.*

Variable	rFVIIa, 20 μg/kg (N=276)	rFVIIa, 80 μg/kg (N=297)	Placebo (N=268)
Death — no. of patients (%)	50 (18)	62 (21)	51 (19)
Odds ratio for survival (95% CI)	0.8 (0.5–1.4)	1.1 (0.7–31.8)	
P value vs. placebo	0.38	0.75	
Modified Rankin scale score†			
Poor outcome (score 5 or 6) — no. of patients (%)	69 (26)	84 (30)	62 (24)
Odds ratio for poor outcome (95% CI)‡	1.0 (0.6–1.6)	1.4 (0.9–2.2)	—
Barthel index score§			
Median	72.5	70.0	70.0
P value vs. placebo	0.54	0.91	—

Mayer et al. *NEJM*. 2008; 358: 2127–2137

Hemostatic treatments: rFVIIa

FAST secondary analysis

In a subgroup of patients

(including those treated early)

the reduction of expansion

with rFVIIa was doubled

Can a Subset of Intracerebral Hemorrhage Patients Benefit From Hemostatic Therapy With Recombinant Activated Factor VII?

Stephan A. Mayer, MD; Stephen M. Davis, MD; Brett E. Skolnick, PhD; Nikolai C. Brun, MD, PhD; Kamilla Begtrup, MSc; Joseph P. Broderick, MD; Michael N. Diringer, MD; Thorsten Steiner, MD

Background and Purpose—In the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial, 80 μg/kg of recombinant activated factor VII (rFVIIa) significantly reduced intracerebral hemorrhage (ICH) expansion when given within 4 hours of onset. However, in contrast to an earlier Phase 2b study, rFVIIa did not improve survival or functional outcome. In this exploratory analysis, we hypothesized that earlier treatment and exclusion of patients with a poor prognosis at baseline might enhance the benefit of rFVIIa treatment.

Methods—Using the FAST data set, the impact of rFVIIa (80 μg/kg) on poor outcome at 3 months (modified Rankin Score of 5 or 6) was systematically evaluated within subgroups using clinically meaningful cut points in onset-to-treatment time, age, and baseline ICH and intraventricular hemorrhage volume. The effect of treatment on outcome was analyzed using logistic regression, and ICH volume was analyzed with linear mixed models.

Results—A subgroup (n=160, 19% of the FAST population) was identified comprising patients ≤70 years with baseline ICH volume <60 mL, intraventricular hemorrhage volume <5 mL, and time from onset-to-treatment ≤2.5 hours. The adjusted ORs for poor outcome with rFVIIa treatment was 0.28 (95% CI, 0.08 to 1.06), whereas the reduction in ICH growth was almost doubled (7.3±3.2 versus 3.8±1.5 mL, P=0.02). The improved effect was confirmed in an analysis of similar Phase 2 patients.

Conclusions—A prospective trial would be needed to determine whether younger patients with ICH without extensive bleeding at baseline can benefit from 80 μg/kg of rFVIIa given within 2.5 hours of symptom onset. (***Stroke*. 2009;40: 833-840.**)

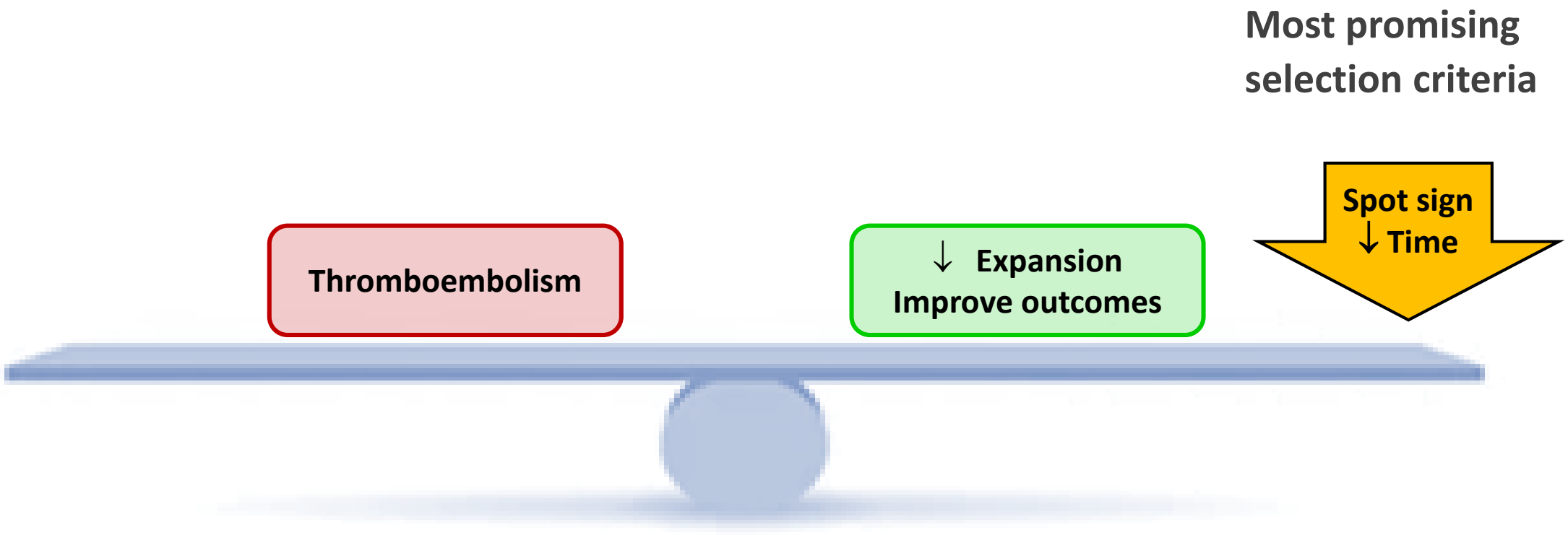
D. Rodriguez-Luna

Hemostatic treatments: patients at highest risk of expansion

Efforts to identify patients at highest risk of expansion have been done in the last few years

↓

Increase the likelihood of demonstrating a clinical benefit of hemostatic treatment



D. Rodriguez-Luna

Hemostatic treatments: selection by *spot sign*

SPOTLIGHT & STOP-IT (rFVIIa)

Merged due to

- Slow recruitment
- Lack of funding

Target sample size not reached (n=69)

No effect on expansion was observed

<6 hours 

<5 hours

Outcome	Median (IQR) rFVIIa (n = 32)	Placebo (n = 37)	*P* Value[a]
Primary outcome			
ICH volume expansion from baseline to 24 h, mL	2.5 (0 to 10.2)	2.6 (0 to 6.6)	.89
Secondary outcome			
ICH plus IVH volume expansion from baseline to 24 h, mL	3.2 (0.1 to 11.5)	4.8 (0 to 7.2)	.91
Additional radiographic outcomes			
ICH volume at 24 h, mL	22.0 (10.0 to 53.0)	29.0 (14.0 to 52.0)	.89
IVH present at 24 h, No. (%)	17 (53)	20 (54)	.94[b]
IVH volume at 24 h, mL	10.2 (5.3 to 14.9)	7.1 (2.1 to 14.2)	.18
IVH volume expansion from baseline to 24 h, mL	−0.2 (−1.2 to 1.6)	1.0 (0 to 4.4)	.18
ICH plus IVH volume at 24 h, mL	25.7 (18.5 to 55.5)	31.0 (15.9 to 59.6)	.91
ICH volume expansion >6 mL or >33% from baseline to 24 h, No. (%)	13 (41)	16 (43)	.83[b]

Gladstone et al. *JAMA Neurol*. 2019; 76: 1493–1501

Hemostatic treatments: selection by *spot sign*

STOP-AUST (TXA)

n=100

ICH <4.5 hours & spot sign

	Placebo (n=50)	Tranexamic acid (n=50)	Effect size (95% CI)	p value
Primary efficacy outcome				
Intracerebral haemorrhage growth*	26 (52%)	22 (44%)	0·72 (0·32 to 1·59)†	0·41
Secondary efficacy outcomes				
Modified Rankin Scale score at 90 days	..	..	1·01 (0·63 to 1·61)‡	0·97
Safety outcomes				
Major thromboembolic events	2 (4%)	1 (2%)	0·49 (0·04 to 5·58)	0·57
Myocardial infarction	0	0	..	..
Pulmonary embolism	1 (2%)	0	..	..
Ischaemic stroke	1 (2%)	1 (2%)	..	..

Meretoja et al. *Lancet Neurol*. 2020; 19: 980–987

Similar expansion and mRS

No ↑ thromboembolism

TRAIGE (TXA)

n=171

ICH <8h & Spot or Black hole or Blend sign

Table 3 Primary and secondary outcomes

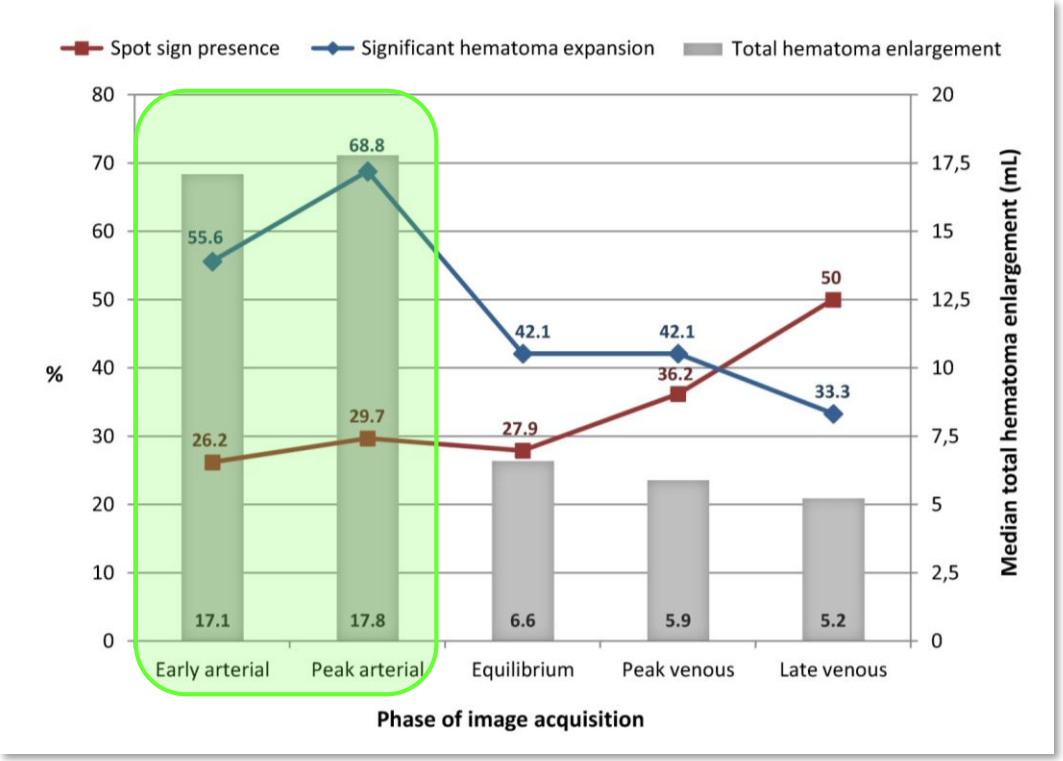
Outcomes	Total (n=171)	TXA (n=89)	Placebo (n=82)	OR (95% CI)	P value
Primary outcome					
Haematoma expansion at 24 hours*, n (%)	70 (40.9)	36 (40.4)	34 (41.5)	0.96 (0.52 to 1.77)	0.89
Secondary outcomes					
mRS at 90 days‡, n (%)					0.78
Major thromboembolic events (ACI) at 90 days†, n (%)	2 (1.2)	1 (1.2)	1 (1.3)		0.96

Liu et al. *Stroke Vasc Neurol*. 2021; 6: 160–169

Hemostatic treatments: selection by *spot sign*

These trials used non-standardized acquisitions of the CTA → **There is a need for standardization**

Single-pase CTA



Rodriguez-Luna et al. *Stroke*. 2014; 45: 734–739

Multiphase CTA

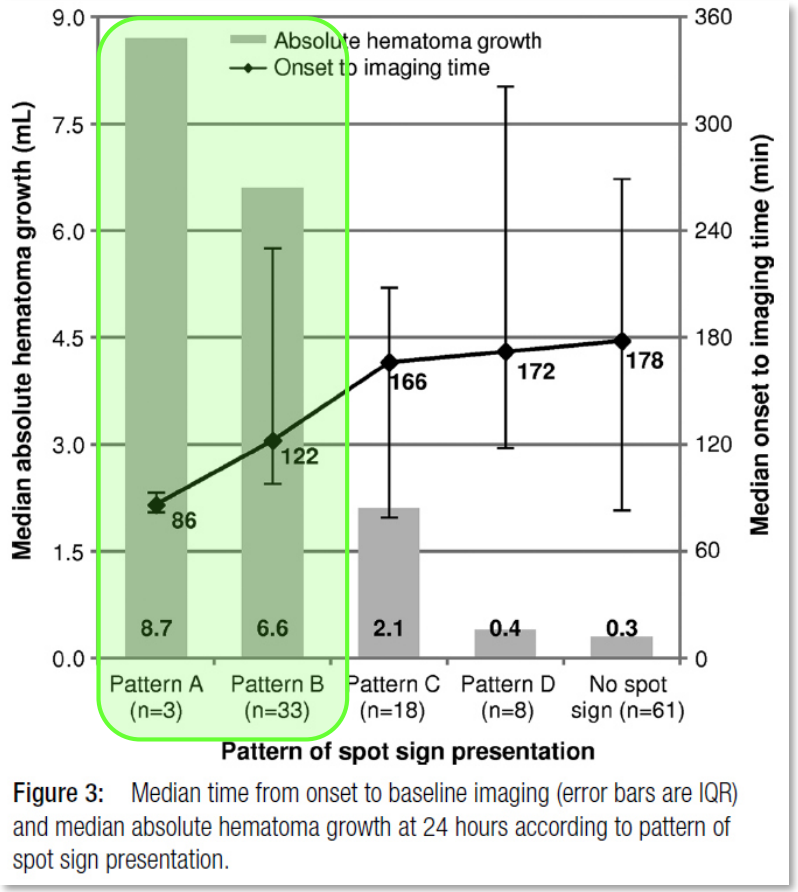


Figure 3: Median time from onset to baseline imaging (error bars are IQR) and median absolute hematoma growth at 24 hours according to pattern of spot sign presentation.

Rodriguez-Luna et al. *Radiology*. 2017; 285: 932–940

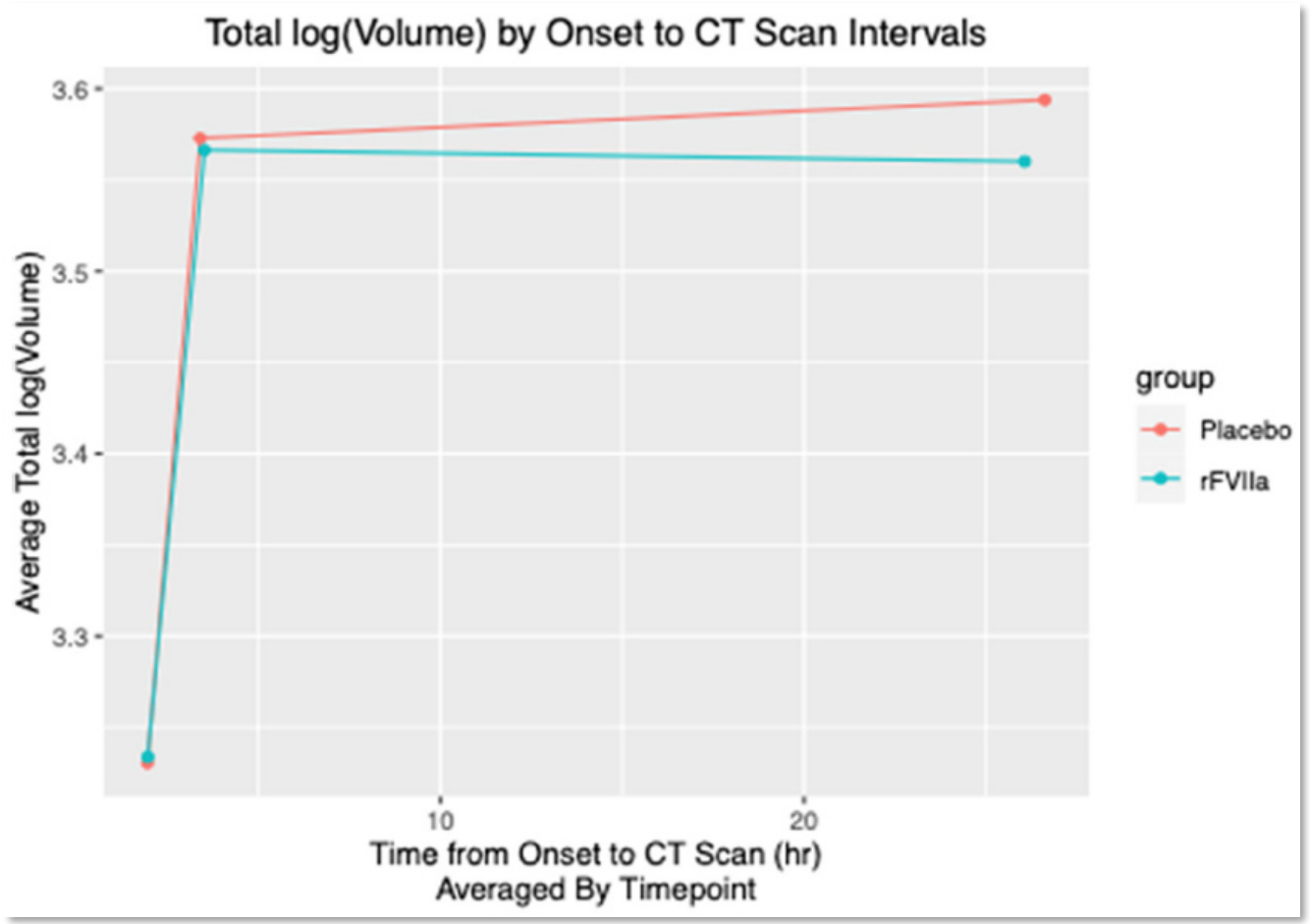
The more arterial the spot sign pattern, the greater expansion

Hemostatic treatments: selection by *spot sign*

SPOTLIGHT prespecified analysis

rFVIIa at 63 min from CT scan

Expansion was already presented in postdose CT



Al-Ajlan et al. *Stroke*. 2023; 54: 715–721

Hemostatic treatments: selection by time

FASTEST

rFVIIa vs. Placebo

ICH <2 hours

Main objective: 180d mRS

Secondary objectives: expansion, quality of life

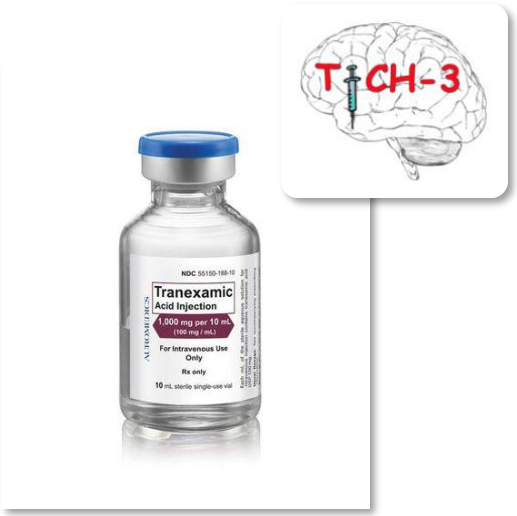
TICH-3

TXA vs. Placebo

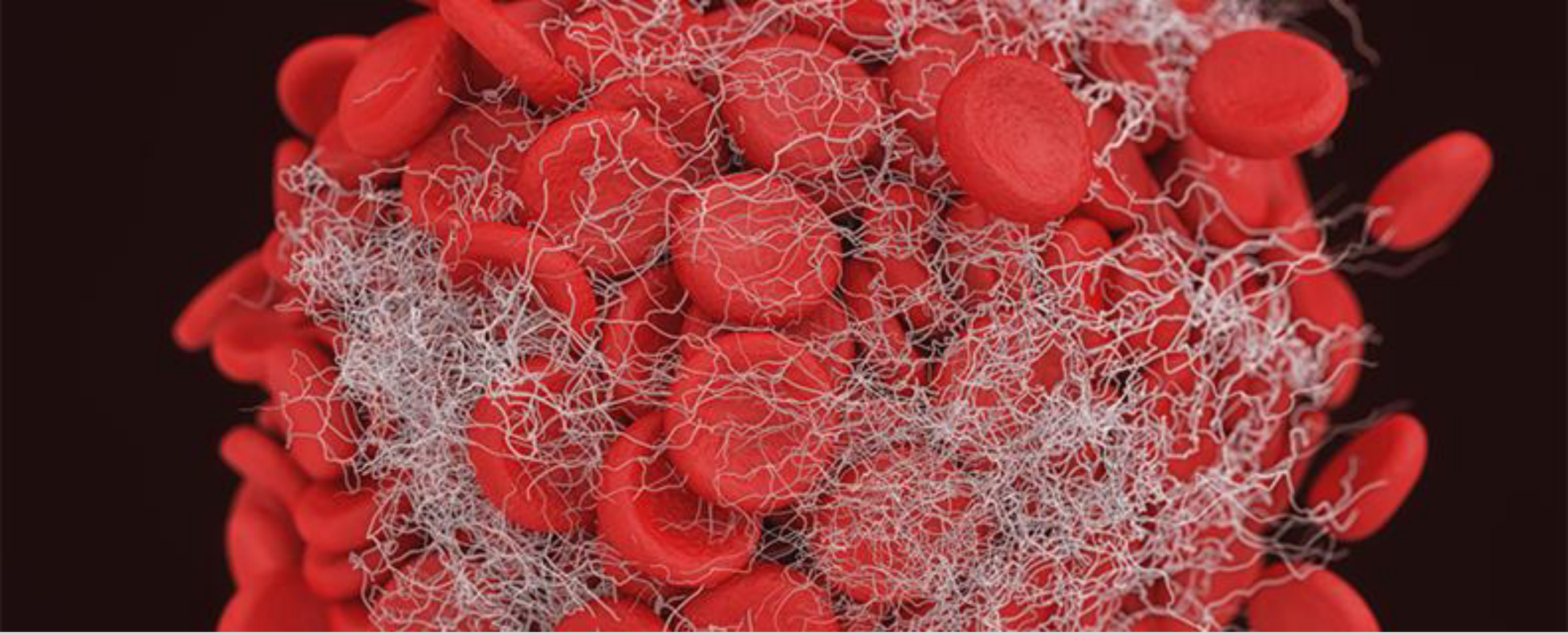
ICH <4.5 hours

Main objective: 7d mortality

Secondary objectives: 180d mRS



D. Rodriguez-Luna



Anticoagulation Reversal

Anticoagulant-related ICH

Up to 20% of all ICH

Poorer outcomes than ICH without anticoagulation

DOACs, compared with warfarin, present smaller ICH and of less severity

Oral anticoagulants reversal strategy

Depends on the anticoagulant agent (different mechanisms of action)

Anticoagunlant		Action	Anticoagulation reversal
Vit K antagonists (**VKAs**)	Warfarin Acenocumarol	Inhibition Vit K dependent coagulation factors (II, VII, IX y X)	Prothrombin complex concentrate (PCC) + Vit K vs. Fresh frozen plasma (FFP)
Direct oral anticoagulants (**DOACs**)	Dabigatran	FIIa inhibition (thrombin)	Idarucizumab
	Rivaroxaban Apixaban Edoxaban	FXa inhibition	Andexanet alfa vs. PCC

Oral anticoagulants reversal: vitamin K antagonists

INCH

4F PCC (30 UI/kg) **+ Vit K** (5–10 mg)

vs. FFP (20 mL/kg)

ICH <12 hours

INR >2

Terminated early in favor of PCC

PCC faster INR normalization

PCC lower hematoma expansion

(underpowered for clinical outcome)

	Fresh frozen plasma (n=23)	Prothrombin complex concentrate (n=27)	Treatment effect (95% CI)	p value
Primary outcome				
INR ≤1·2 within 3 h	2 (9%)	18 (67%)	OR 30·6 (4·7 to 197·9)*	0·0003
Secondary clinical outcomes				
Deaths at day 90	8 (35%)	5 (19%)	No proportional hazard assumed	0·14†
Functional independence (mRS score 0–3)				
At day 15 or discharge	7 (30%)	7 (26%)	OR 2·3 (0·5 to 13·1)*	0·31
At day 90	9 (39%)	10 (37%)	OR 1·7 (0·4 to 6·8)*	0·47
NIHSS score at day 15 or discharge	10·9	12·2	−1·9 (−8·3 to 4·4)‡	0·53
Barthel index at day 90	52·5 (40·3)	70·0 (37·7)	−16·0 (−44·9 to 12·8)‡	0·27
Quality of life at day 90§	8·21	9·25	−0·7 (−5·6 to 4·2)‡	0·78
Extended Glasgow Outcome Scale at day 90	4·60	4·18	0·39 (−0·84 to 1·63)‡	0·52
Secondary imaging outcomes				
Time until INR ≤1·2 normalisation of INR (min)	1482 (1335–1610)	40 (30–1610)	No proportional hazard assumed	0·050†
Imaging data at 3 h¶				
Haematoma expansion (mL)	23·7 (28·4)	9·7 (20·9)	16·9 (2·5 to 31·3)‡	0·023
≥15% growth‖	16/22 (73%)**	15/26 (58%)**	OR 2·0 (0·6 to 7·3)*	0·29
≥33% growth‖	13/22 (59%)**	12 (44%)**	OR 3·8 (1·1 to 16·0)*	0·048
Imaging data at 24 h				
Haematoma expansion (mL)	22·1 (27·1)	8·3 (18·3)	16·4 (2·9 to 29·9)‡	0·018
≥15% growth or death‖	14/20 (70%)††	12/27 (44%)	OR 3·9 (1·0 to 17·6)*	0·044
≥33% growth or death‖	12/20 (60%) ††	8/27 (30%)	OR 4·8 (1·3 to 20·4)*	0·024
Secondary exploratory outcomes				
Time from onset to baseline CCT (min)	202 (152)	199 (160)	−6 (−98 to 90)‡	0·90
Time from baseline CCT to start of treatment (min)	80 (33)	59 (20)	26 (13 to 39)‡	0·0002
Duration of infusion (min)	129 (69)	34 (31)	103 (75 to 130)‡	<0·0001

Steiner et al. *Lancet Neurol*. 2016; 15: 566–573

Oral anticoagulants reversal: Dabigatran

No RCT

RE-VERSE AD

Single-arm prospective study

Idarucizumab (2.5 + 2.5 mg)

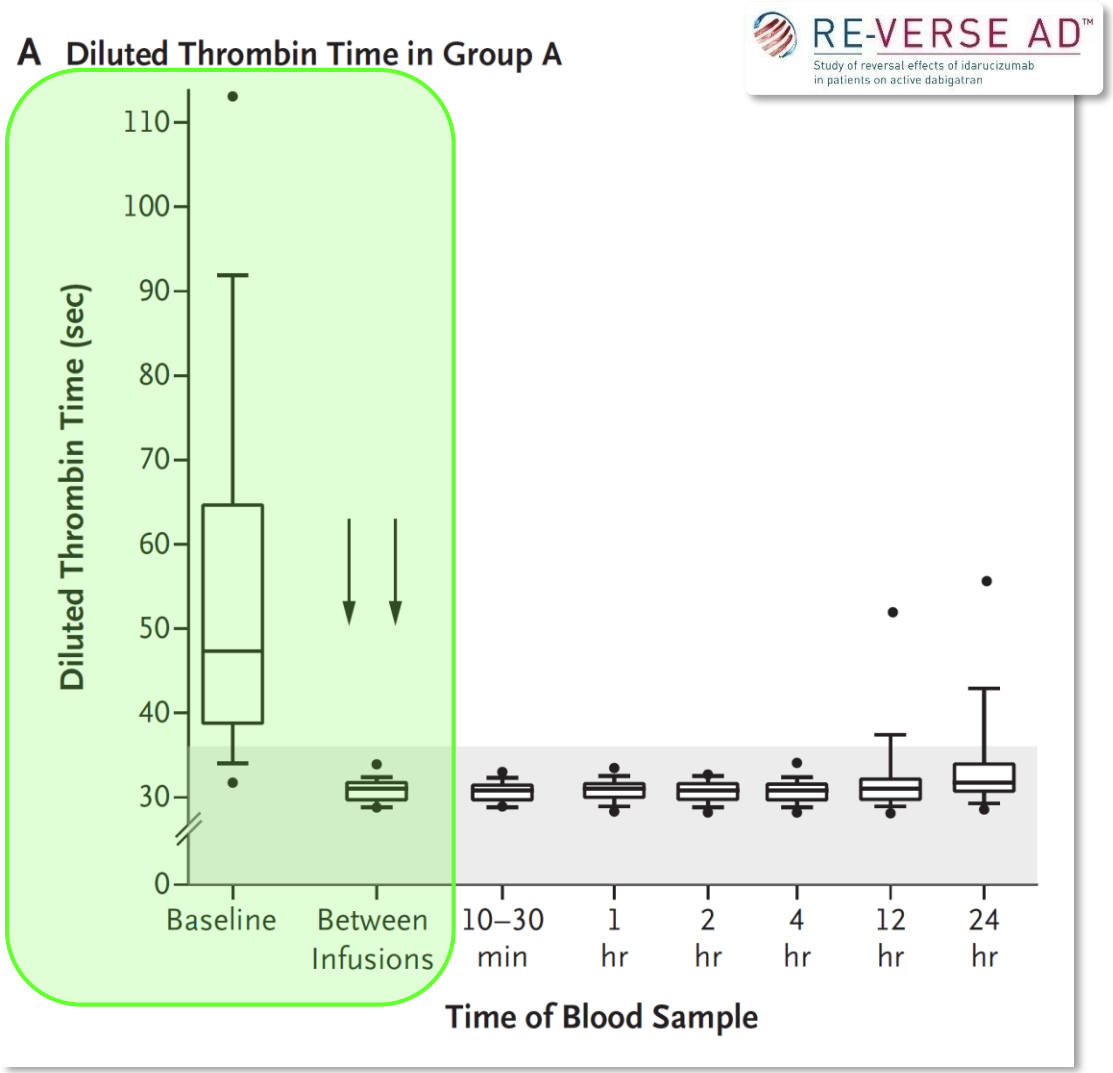
503 major hemorrhage or recent surgery

301 major hemorrhage

53 ICH

100% reversal <4 hours

Lower mortality compared with previous studies



Pollack et al. *NEJM*. 2017; 377: 431–441

Oral anticoagulants reversal: factor Xa inhibitors

ANNEXa-I

Andexanet alfa vs. Standard (PCC included)

900 ICH <6 hours

Apixaban, Rivaroxaban o Edoxaban <15h

Terminated early in favor of andexanet alfa (n=530)

Superiority in hemostatic efficacy

Despite ↑ thromboembolisms

Underpowered to mRS score

End Point	Andexanet (N=224)	Usual Care (N=228)	Adjusted Difference per 100 Patients (95% CI)*	P Value*
	no./total no. (%)		*percentage points*	
Hemostatic efficacy	150/224 (67.0)	121/228 (53.1)	13.4 (4.6 to 22.2)	0.003
Hematoma volume change ≤35%†	165/215 (76.7)	137/212 (64.6)	12.1 (3.6 to 20.5)	
NIHSS score change <7 points	188/214 (87.9)	181/218 (83.0)	4.6 (–2.0 to 11.2)	
No receipt of rescue therapy between 3 hr and 12 hr	218/224 (97.3)	213/228 (93.4)	3.8 (0.0 to 7.6)	
Hematoma volume increase ≥12.5 ml‡	24/216 (11.1)	36/214 (16.8)	–5.6 (–12.0 to 0.8)	
Hemostatic efficacy, excluding patients nonevaluable for administrative reasons	150/218 (68.8)	121/225 (53.8)	14.5 (5.7 to 23.4)	

Event	Andexanet (N=263)	Usual Care (N=267)	Increase per 100 Patients (95% CI)†	P Value†
	no. of patients (%)		*percentage points*	
≥1 Thrombotic event	27 (10.3)	15 (5.6)	4.6 (0.1 to 9.2)	0.048
Transient ischemic attack	0	0	—	
Ischemic stroke	17 (6.5)	4 (1.5)	5.0 (1.5 to 8.8)	
Myocardial infarction	11 (4.2)	4 (1.5)	2.7 (–0.2 to 6.1)	
Deep-vein thrombosis	1 (0.4)	2 (0.7)	–0.4 (–2.4 to 1.5)	
Pulmonary embolism	1 (0.4)	6 (2.2)	–1.9 (–4.5 to 0.2)	
Arterial systemic embolism	3 (1.1)	2 (0.7)	0.4 (–1.7 to 2.7)	
Death	73 (27.8)	68 (25.5)	2.5 (–5.0 to 10.0)	0.51

Conolly et al. *NEJM*. 2024; 390: 1745–1755

Oral anticoagulants reversal: Application to real clinical practice

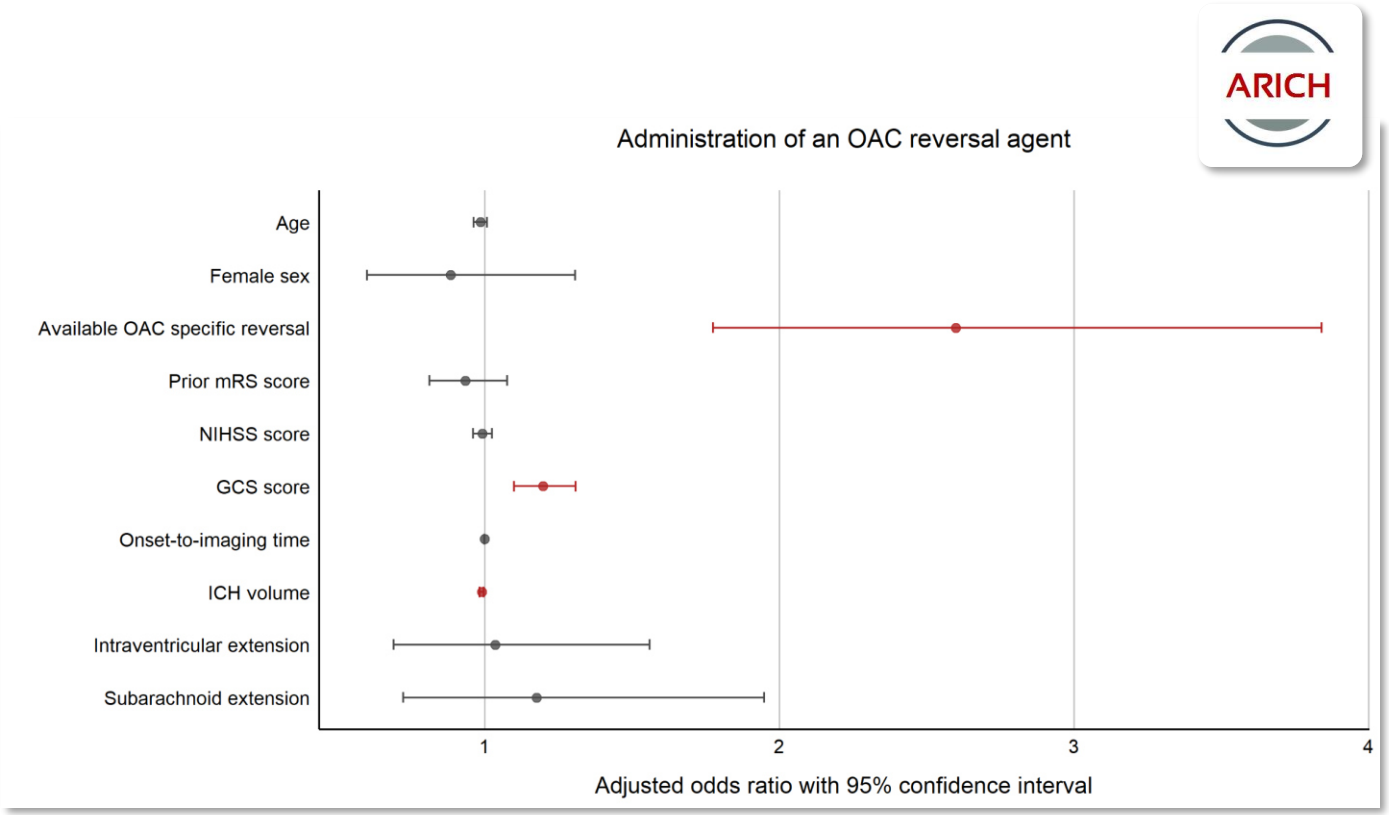
In Spain there is no availability of andexanet alfa

ARICH registry

Spanish registry of OAC-related ICH

18 stroke centers

867 OAC-related ICH <24 hours



Rodriguez-Luna et al. *Unpublished data*

Determinants of No anticoagulant reversal

↓ GCS score

↑ ICH volume

Unavailability of a specific reversal agent → need to ensure the availability of specific agents

Oral anticoagulants reversal: Influence of time

AHA GWTG registry

5224 ICH pt under OAC

Door-to-treatment time ≤60 min vs. clinical and functional outcomes

Table 2. Association of Door-to-Treatment (DTT) Time of 60 Minutes or Less vs More Than 60 Minutes With Clinical Outcomes

	No./total No. (%)		OR (95% CI)		Patients included in model, No.	
Outcome	DTT time ≤60 min	DTT time >60 min	Unadjusted	Adjusted	Unadjusted	Adjusted
In-hospital mortality	462/1449 (31.9)	1082/3775 (28.7)	1.15 (1.00-1.31)	0.83 (0.69-1.00)	5224	3453
In-hospital mortality or hospice discharge	668/1449 (46.1)	1556/3775 (41.2)	1.22 (1.08-1.38)	0.82 (0.69-0.99)	5224	3453
mRS score of 0-2 vs 3-6	66/1140 (5.8)	258/2907 (8.9)	0.63 (0.47-0.84)	1.04 (0.70-1.56)	4047	2737
mRS score of 0-3 vs 4-6	121/1140 (10.6)	484/2907 (16.6)	0.59 (0.47-0.73)	0.91 (0.67-1.24)	4047	2737
mRS score of 0-4 vs 5-6	387/1140 (33.9)	1168/2907 (40.2)	0.75 (0.65-0.88)	1.19 (0.96-1.48)	4047	2737
Ambulatory with or without assistance	384/966 (39.8)	1201/2443 (49.2)	0.66 (0.57-0.78)	1.13 (0.91-1.42)	3409	2358
Discharged home or to inpatient rehabilitation	449/1449 (31.0)	1381/3775 (36.6)	0.77 (0.68-0.88)	1.23 (1.02-1.49)	5224	3453

Sheth et al. *JAMA Neurology*. 2024; 81: 363–372

Surgical Evacuation of ICH

Surgical evacuation of ICH

Potential Benefits

↓ mass effect, ↓ intracranial pressure, improvement of cerebral perfusion

↓ secondary cytotoxic damage

Potential Risks

Dissecting healthy brain tissue

Complications: hemorrhage, infection

Options

Open craniotomy (with ICH evacuation)

Minimally invasive surgery (ICH evacuation ± thrombolysis)

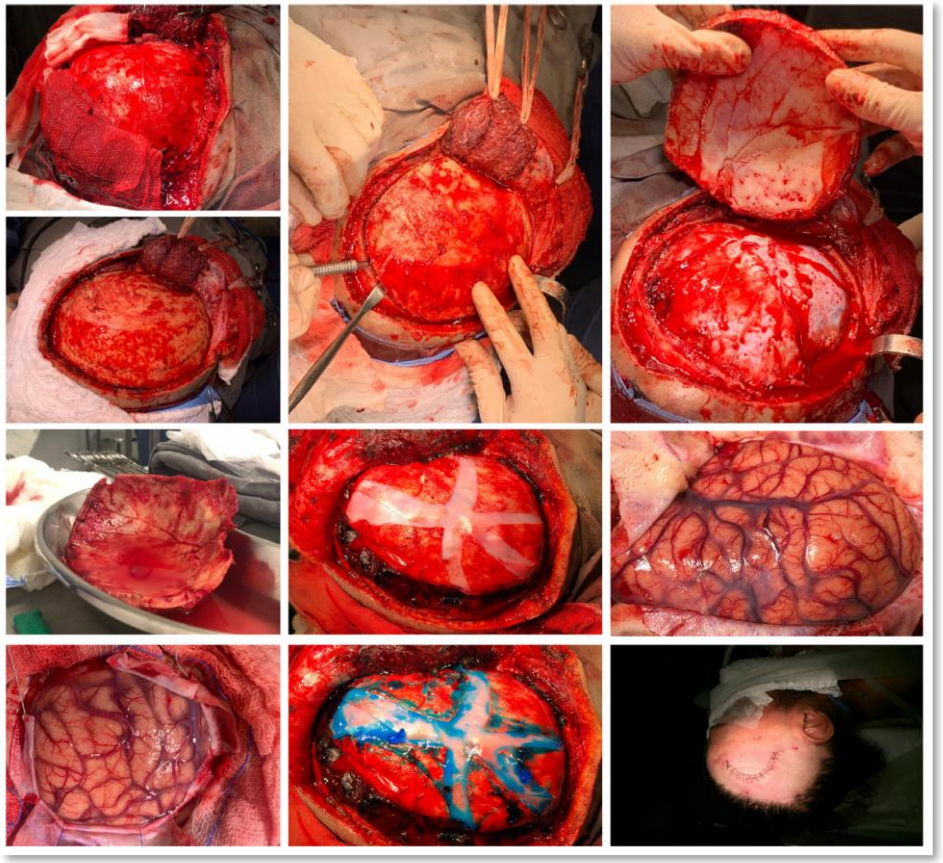
Results

One positive trial of minimally invasive surgery (ENRICH)

Open craniotomy with hematoma evacuation

Most used technique (accessibility)

Most studied technique



de Oliveira Manoel. *Crit Care*. 2020;24: 45

Large trials

STICH: supratentorial ICH <72h

	Early surgery (n=468)	Initial conservative treatment (n=497)	Absolute benefit (95% CI)
Primary outcome			
Favourable	122 (26%)	118 (24%)	2·3 (−3·2 to 7·7)
Unfavourable	346 (74%)	378 (76%)	..
Not recorded		1	..

Mendelow et al. *Lancet.* 2005; 365: 387–397

STICH II: superficial lobar ICH <48h, no IVH

	Early surgery group	Initial conservative treatment group	p value	Absolute difference (95% CI)
Primary outcome	297	286		
Prognosis based			0·367*	3·7% (−4·3 to 11·6)
Unfavourable	174 (59%)	178 (62%)	..	..
Favourable	123 (41%)	108 (38%)	..	..

Mendelow et al. *Lancet.* 2013; 382: 397–408

Minimally Invasive Surgery (MIS)

Advantages (compared to open craniotomy)

- Minimization of damage
- Reduction of intervention time
- Possibility of only using local anesthetic

Disadvantages

- Incomplete evacuation of the hematoma
- Potential risk of rebleeding (due to the use of fibrinolytics)
- ↑ risk of infection (due to the catheter)

Main trials

- MISTIE III
- ENRICH

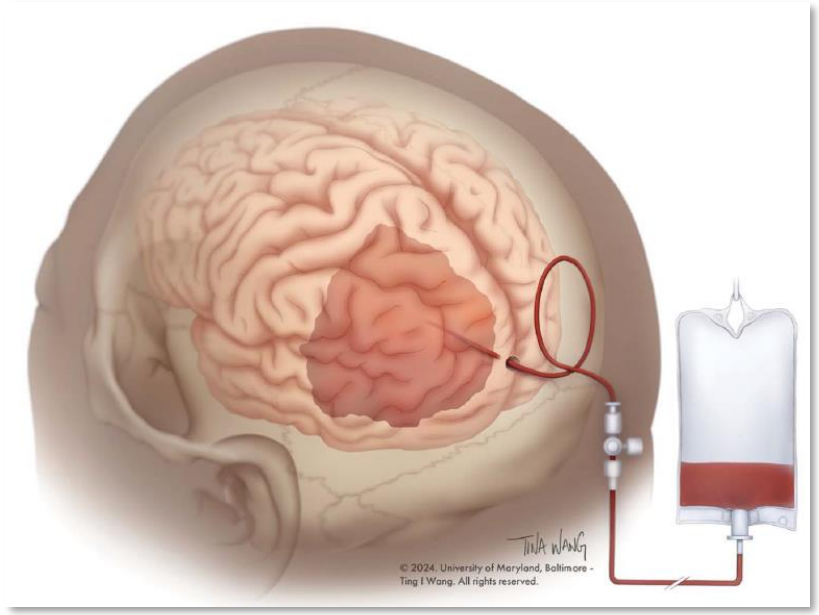
MIS: Stereotactic aspiration and thrombolysis

MISTIE III

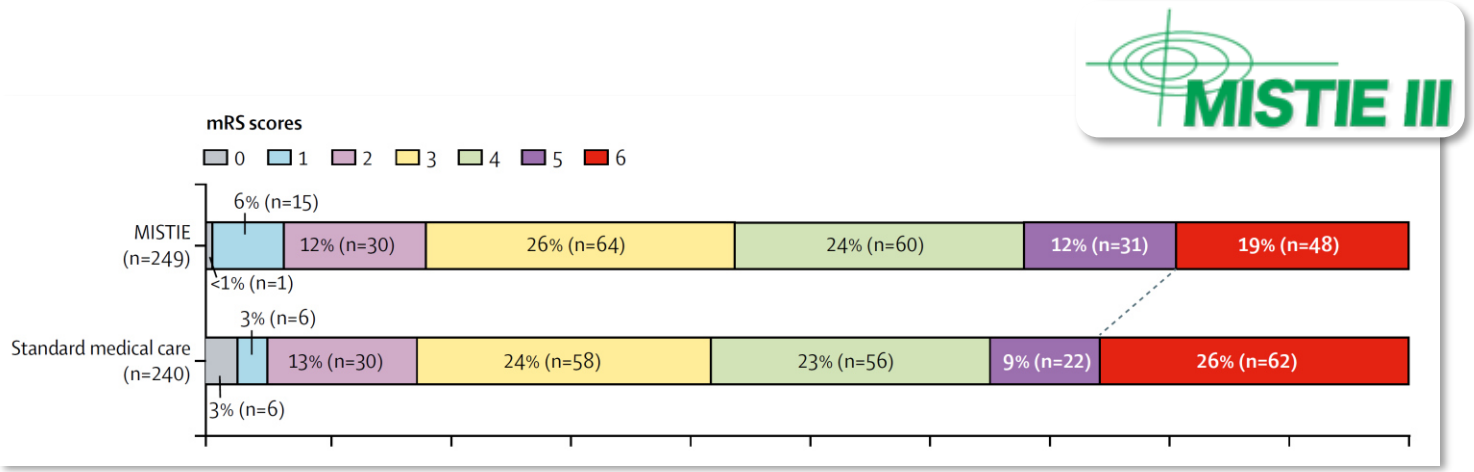
Supratentorial ICH <24h

Starting treatment 12–72h after CT

Minimally invasive catheter evacuation + rtPA vs. standard



Morris et al. *Neurology.* 2024, 103: e209714



Hanley et al. *Lancet.* 2019, 393: 1021–1032

MIS: Endoport mediated evacuation

ENRICH

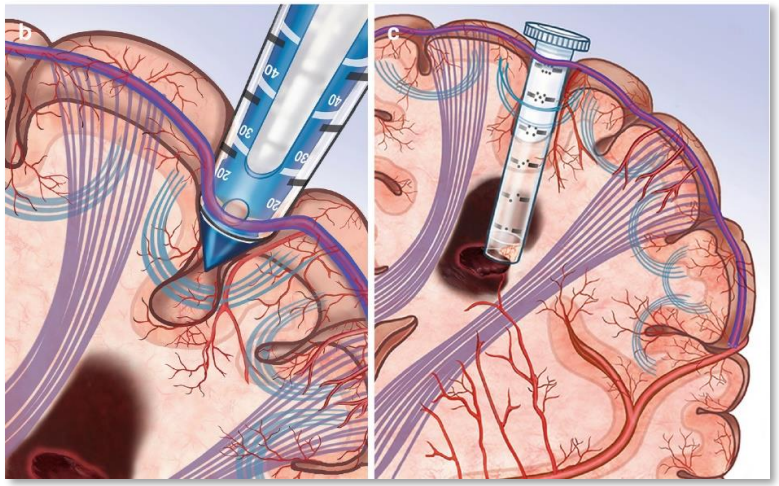
ICH <24 hours

Transulcal parafascicular evacuation with BrainPath Endoport Sheath® vs. Standard treatment

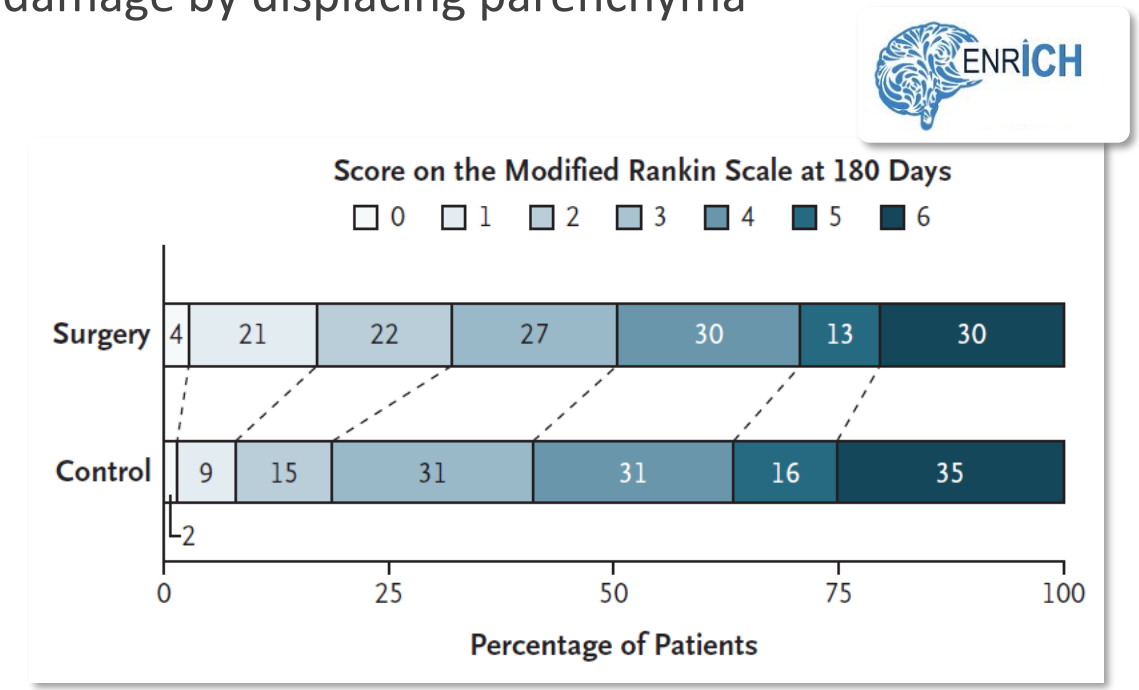
The sheath has an obturator with a tip that minimizes damage by displacing parenchyma

Once hematoma is reached, the obturator is removed

Hematoma is evacuated by irrigation and suction



Vargas et al (2019) Spontaneous Intracerebral Hemorrhage. In: Spiotta et al. Management of Cerebrovascular Disorders.

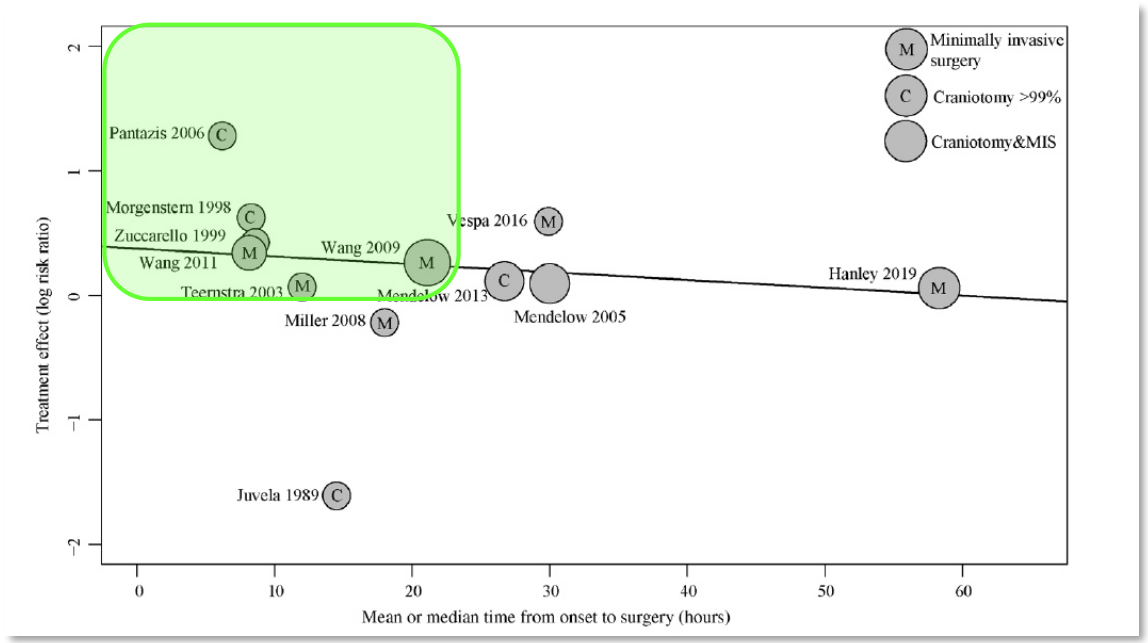


Pradilla et al. *NEJM.* 2024, 390: 1277–1289

Surgical evacuation of ICH. Influence of time

Meta-analysis (MIS and/or craniotomy)

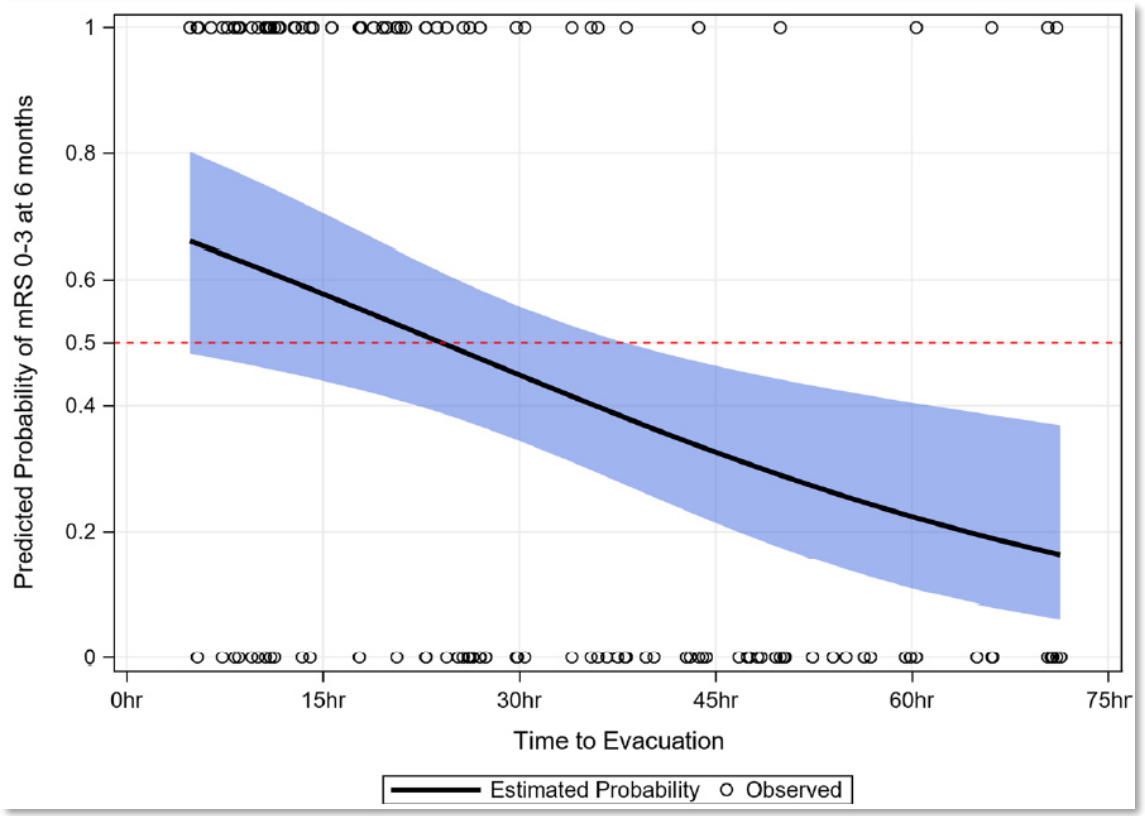
Benefit of surgery was stronger when performed sooner



Sondag et al. *Ann Neurol.* 2020, 88: 239–250

Single center study (MIS)

Shorter time was related to better outcomes



Kellner et al. *Stroke.* 2021, 52: e546–e539

How should we implement all these approaches?

Bundled care

Definition of a Bundle

A small set of evidence-based interventions for a defined patient segment/population and care setting that, when implemented together, will result in significantly better outcomes than when implemented individually.

Institute for Healthcare Improvement, 2001

Aim: To facilitate implementation of evidenced-based practice by ensuring that **all components** of the bundle are considered an delivered effectively **to every patient**

Bundled care

QASC

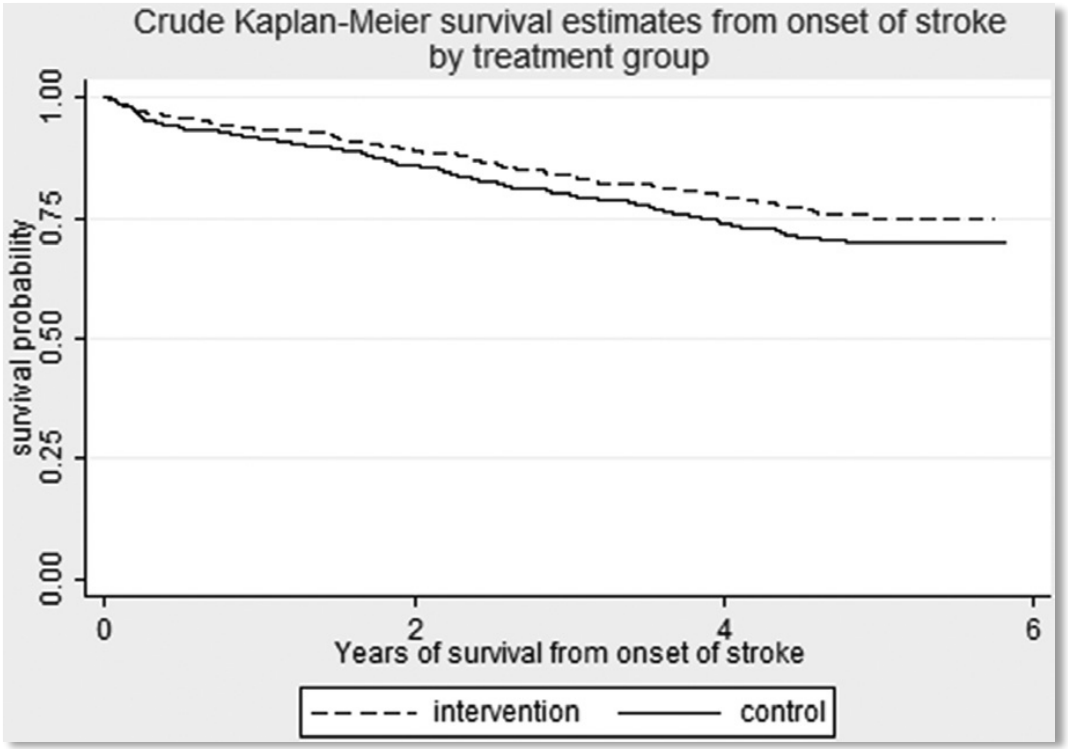
Ischemic and hemorrhagic stroke

Nursing protocol to manage:

- Fever
- Hiperglycemia
- Swallowing dysfunction

↓ Disability and mortality at both 90 days and 4 years

QASC
Quality in Acute Stroke Care



Middleton et al. *Stroke*. 2017, 48: 1331–1336

Bundled care

ABC

Anticoagulation: Rapid anticoagulation reversal

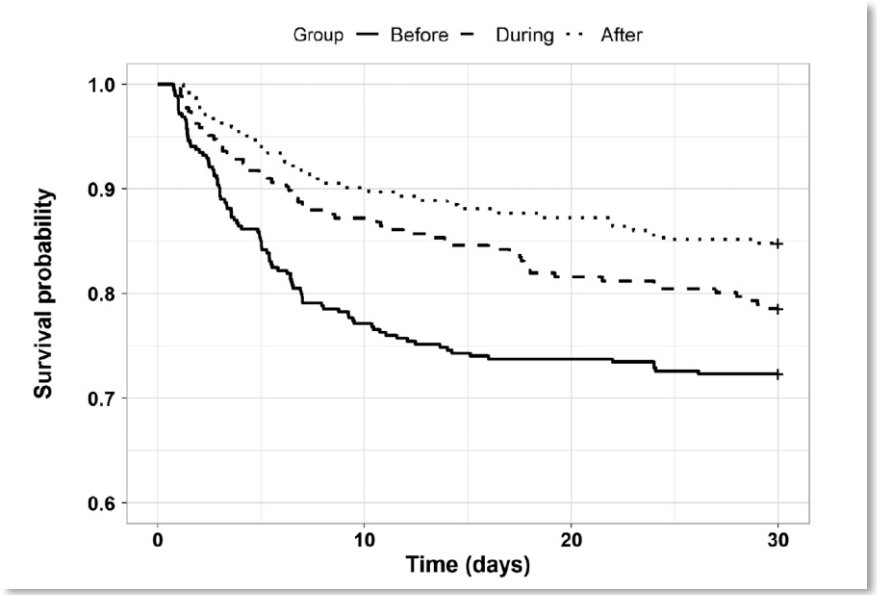
Blood pressure: SBP lowering <140 mmHg within 1st hour

Care pathway: Immediate neurosurgical referral:

- GCS <9
- Posterior fossa
- Obstructed 3rd-4th ventricle
- ICH volume >30 mL

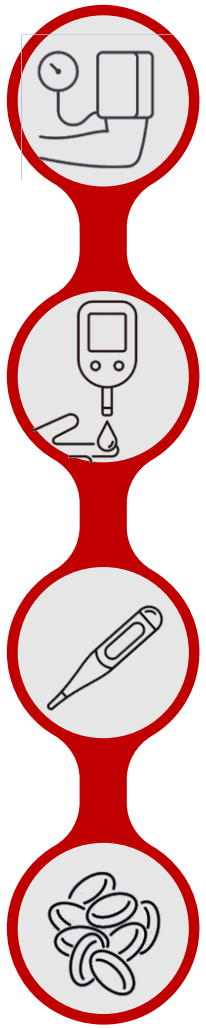
↓ BP needle-to-target times

↓ Mortality at 30 days



Parry-Jones et al. *Ann Neurol*. 2019, 86: 495–503

Bundled care

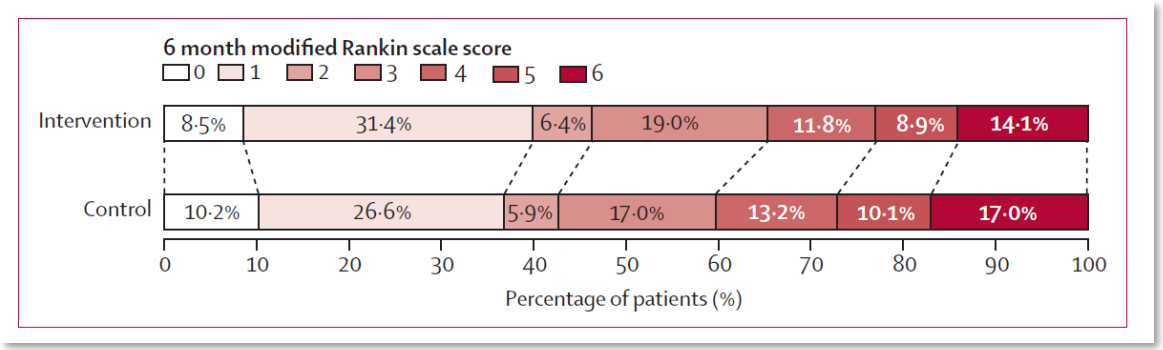


INTERACT3

Definitive support for this comprehensive approach

- Intensive BP lowering
- Strict glucose control
- Antipyrexia treatment
- Reversal of warfarin-related anticoagulation

Improved functional outcome at 6 months



Ma et al. *Lancet*. 2023; 402: 27–40

Implementation Challenges

Implementation challenges

Implementing a Goal-Directed Care Bundle after Acute Intracerebral Haemorrhage: Process Evaluation for the Third INTEnsive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial Study in China

Keywords
Process evaluation · Clinical trial · Care bundle · Management · Intracerebral haemorrhage · Stroke

Abstract

Background: The third INTEnsive care bundle with blood pressure Reduction in Acute Cerebral Haemorrhage Trial is an ongoing international, multicentre, stepped wedge, cluster-randomized trial to determine the effectiveness of a goal-directed care bundle (early intensive blood pressure [BP] lowering, glycaemic control, treatment of pyrexia, and reversal of anticoagulation), as compared to standard of care, on patient-centred outcomes after acute intracerebral haemorrhage (ICH). An embedded process evaluation aims to identify factors related to the uptake and implementation of the intervention. Herein, we present the process evaluation results for hospital sites in China. ***Methods/Design:*** A mixed methods approach, including surveys, focused group discussions and interviews with clinicians, routine monitoring, and recruitment logs were used to collect data across purposively sampled hospitals. Medical Research Council guidance and normalization process theory were used as theoretical frameworks for design, data analysis, and synthesis. ***Results:*** Twenty quantitative surveys were completed with clinicians, and 26 interviews and 2 focus group discussions were conducted during 2019–2020. The care bundle was generally delivered as planned and acceptable by doctors and nurses, but difficulties were reported in achieving the protocol-defined target levels of BP and glycaemic control. Resistance to implementing the care bundle occurred for patients perceived to be at high risk of adverse effects. Common organizational contextual factors that impeded implementation included delayed processes and limited medication supply, while es-

Trial registration: ClinicalTrials.gov NCT03209258, registered on July 1, 2017. Chinese Trial Registry ChiCTR-IOC-17011787, registered on June 28, 2017.

Ouyang et al. *Cerebrovasc Dis*. 2022; 51: 373–383

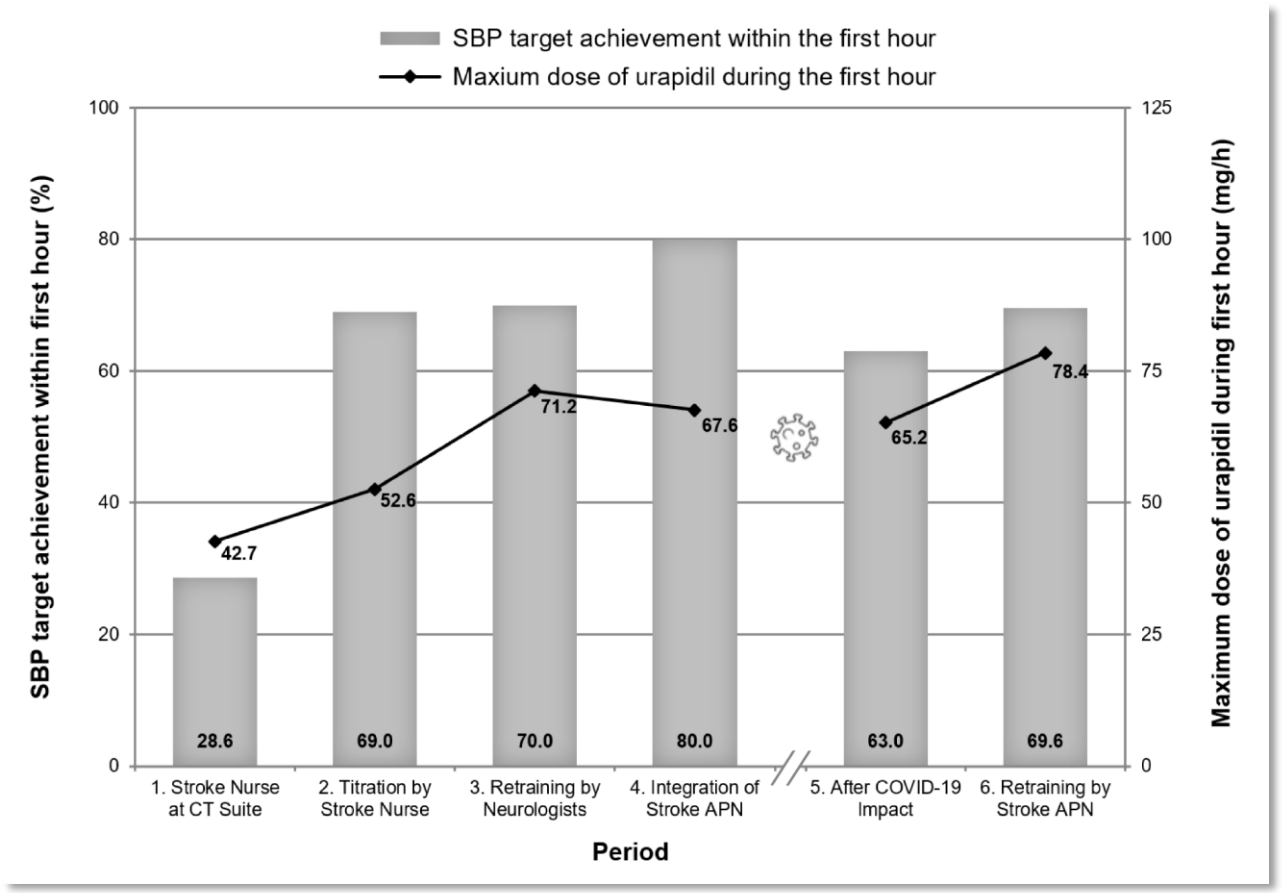
Implementation challenges

Vall d'Hebron ICH experience

Changes in nursing care

- Progressive shift towards nurses taking the lead in BP management
- Continuous education

Improve time metrics and BP outcomes



Pancorbo et al. *J Clin Nurs*. 2024; 33: 1398–1408

Challenges. Access to a Stroke Unit

Optimal environment

Staff expertise

Nursing care

Multiparametric monitorization

Prevention of complications

Diagnostic procedures

Early mobilization

↓ ESO EUROPEAN STROKE ORGANISATION

Stroke Unit

(pt that do not require ICU care)

Cerebrovascular Diseases

Acute Ischemic Stroke Treatment:
State of the Art and New Options

Cerebrovasc Dis 2001;11(suppl 1):31–39

**Acute Care in Stroke:
Do Stroke Units Make the Difference?**

E. Díez-Tejedor B. Fuentes

Stroke Unit, Department of Neurology, Hospital Universitario La Paz, Universidad Autónoma de Madrid, Spain

Stroke unit admission is associated with better outcome and lower mortality in patients with intracerebral hemorrhage

M. N. Ungerer[a], P. Ringleb[a], B. Reuter[b], C. Stock[c], F. Ippen[a], S. Hyrenbach[d], I. Bruder[d], P Martus[e], C. Gumbinger[a] and the AG Schlaganfall

[a]*Department of Neurology, University Hospital Heidelberg, Heidelberg;* [b]*Helios Klinik Müllheim, Müllheim;* [c]*Institute of Medical Biometry and Informatics (IMBI), University of Heidelberg, Heidelberg;* [d]*Qualitätssicherung im Gesundheitswesen Baden-Wuerttemberg (GeQiK Baden-Wuerttemberg), Stuttgart; and* [e]*Institute for Clinical Epidemiology and Applied Biometry, University of Tuebingen, Tuebingen, Germany*

Keywords:
admission ward, intracerebral hemorrhage, stroke unit

Received 3 November 2019
Accepted 3 February 2020

European Journal of Neurology 2020, **27:** 825–832

doi:10.1111/ene.14164

Background and purpose: There is no clear consensus among current guidelines on the preferred admission ward [i.e. intensive care unit (ICU) or stroke unit (SU)] for patients with intracerebral hemorrhage. Based on expert opinion, the American Heart Association and European Stroke Organization recommend treatment in neurological/neuroscience ICUs (NICUs) or SUs. The European Stroke Organization guideline states that there are no studies available directly comparing outcomes between ICUs and SUs.
Methods: We performed an observational study comparing outcomes of 10 811 consecutive non-comatose patients with intracerebral hemorrhage according to admission ward [ICUs, SUs and normal wards (NWs)]. Primary outcomes were the modified Rankin Scale score at discharge and intrahospital mortality. An additional analysis compared NICUs with SUs.
Results: Treatment outside an SU was associated with higher odds for an unfavorable outcome [ICU vs. SU: odds ratio (OR), 1.27; 95% confidence interval (CI), 1.09–1.46; NW vs. SU: OR, 1.28; 95% CI, 1.08–1.52] and higher odds for intrahospital mortality (ICU vs. SU: OR, 2.11; 95% CI, 1.75–2.55; NW vs. SU: OR, 1.52; 95% CI, 1.23–1.89). A subgroup analysis of severely affected patients treated in dedicated NICUs (vs. SUs) showed that they had a lower risk of a poor outcome (OR, 0.45; 95% CI, 0.26–0.79).
Conclusions: Treatment in SUs was associated with better functional outcome and reduced mortality compared with ICUs and NWs. Our findings support the current guideline recommendations to treat patients with intracerebral hemorrhage in SUs or NICUs and suggest that some patients may further benefit from NICU treatment.

Challenges. Code ICH

Expert consensus

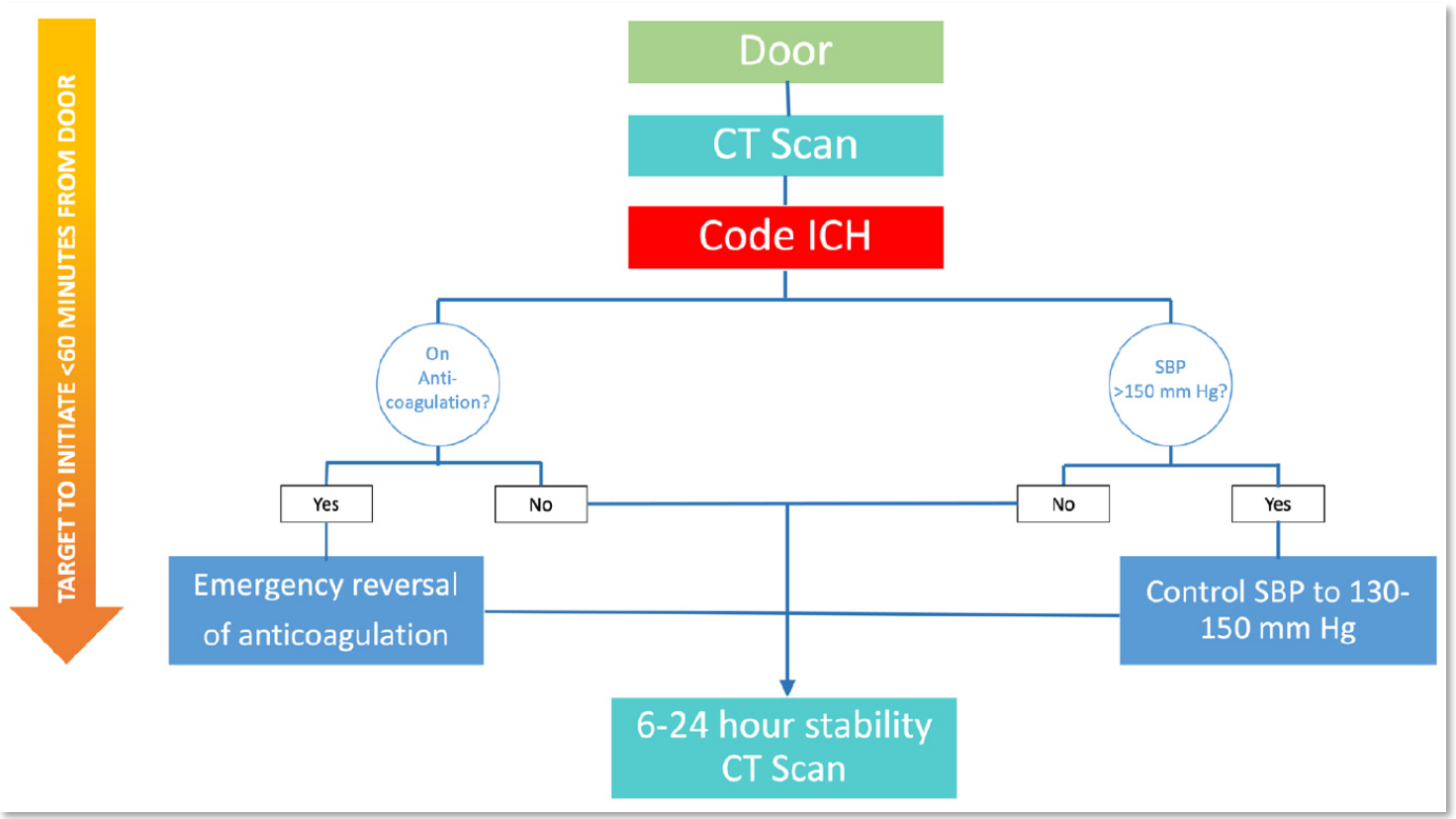
To help address some of these challenges

Imperative for timely intervention

- BP control
- Reversal of anticoagulation

Proposal

- ICH workflow
- Time-based metrics



Li et al. *Stroke*. 2024; 55: 494–505

WHOM

Every acute ICH patient

WHAT

All components of a care bundle: BP control, OAC reversal, access to neurosurgical evaluation, glucose control, temperature control, swallowing evaluation, etc.

WHEN

As soon as possible, especially for BP control and OAC reversal 

WHERE

At the bedside, ideally initiated in the CT suite and continued at the Stroke Unit

WHY

ICH is a treatable disease: care bundle with BP control, OAC reversal, MIS for lobar ICH

HOW

Challenges: code ICH (time metrics), role of nursing staff, access to the Stroke Unit

RICORS-ICTUS | Instituto de Salud Carlos III

Time is brain! in intracerebral hemorrhage

Prof. David Rodriguez-Luna, MD, PHD

Department of Neurology, Vall d'Hebron University Hospital, Barcelona

Stroke Research Group, Vall d'Hebron Research Institute, Barcelona

Department of Medicine, Autonomous University of Barcelona, Barcelona

Vall d'Hebron Barcelona Hospital Campus | Vall d'Hebron Hospital Universitari | Vall d'Hebron Institut de Recerca | UAB Universitat Autònoma de Barcelona

david.rodriguez@vallhebron.cat