

# Advances in the Treatment of Intracerebral Hemorrhage

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# Disclosures

- No relevant disclosures
- NIH funding for basic/translational ICH research
  - K08NS078110, R21NS088972

# Intracerebral Hemorrhage (ICH)

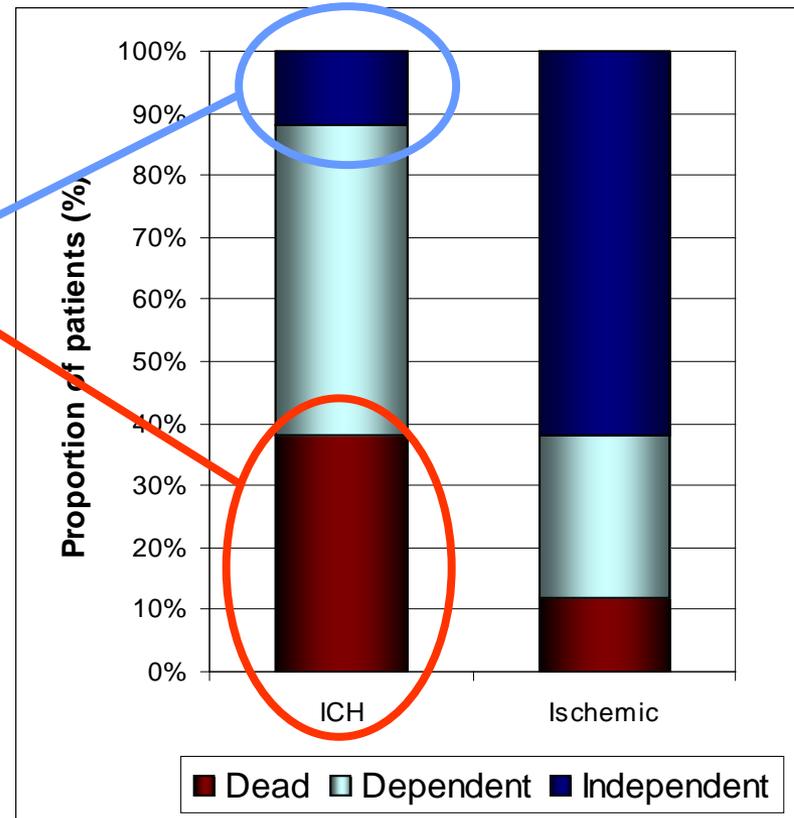


# Traditionally High Mortality and Limited Recovery Post-ICH

- **Mortality**

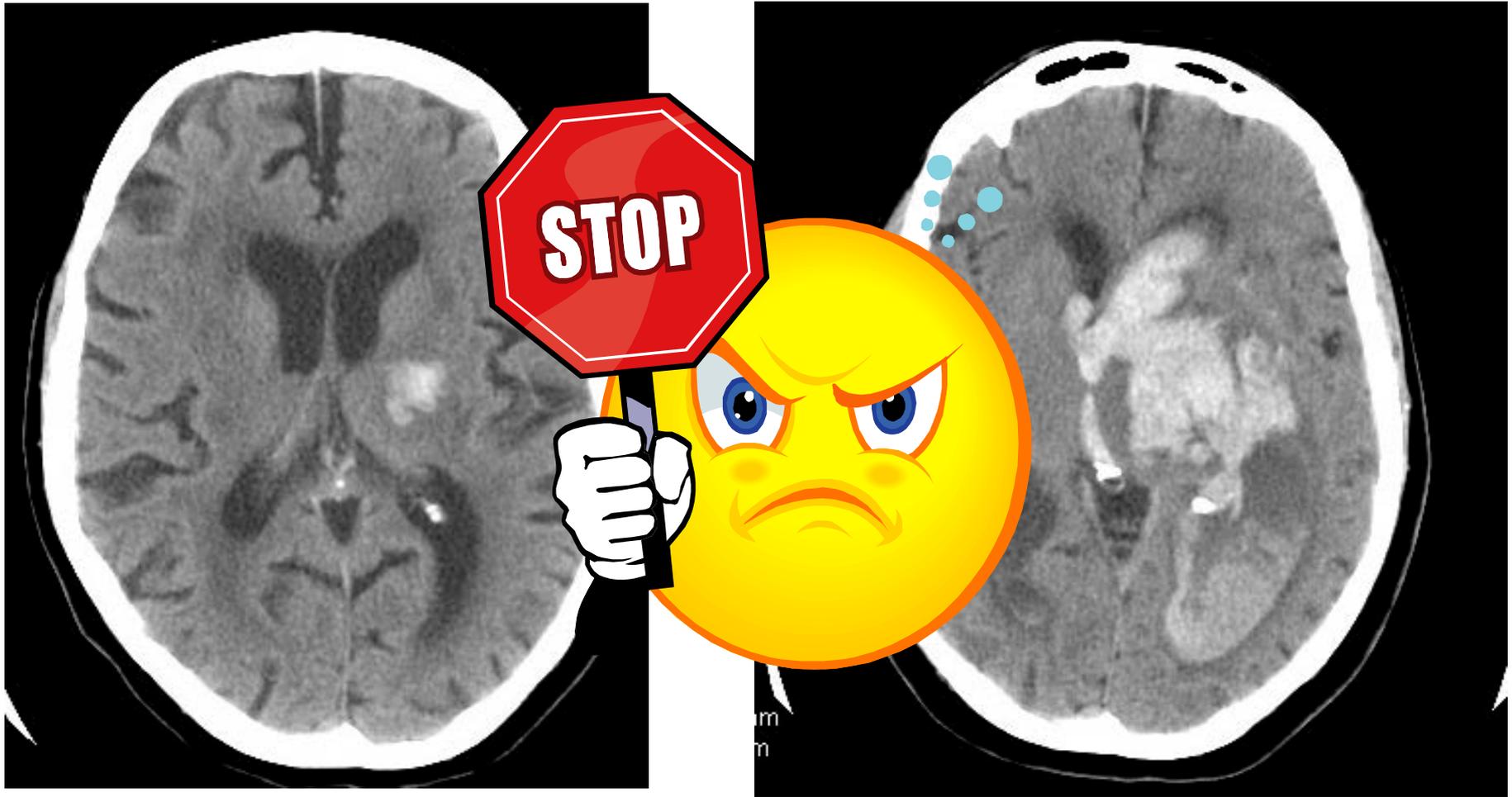
- 6 month 30-50%

- **Only 20% of ICH patients are independent at 6 months vs 60% of ischemic stroke patients**



Manno EM, et al. *Mayo Clin Proc.* 2005;80:420-433; Mayer SA, Rincon F. *Lancet Neurol.* 2005;4:662-672; Qureshi AI, et al. *N Engl J Med.* 2001;344:1450-1460; Taylor TN, et al. *Stroke.* 1996;27:1459-1466; Reed SD, et al. *Neurology.* 2001;57:305-314.

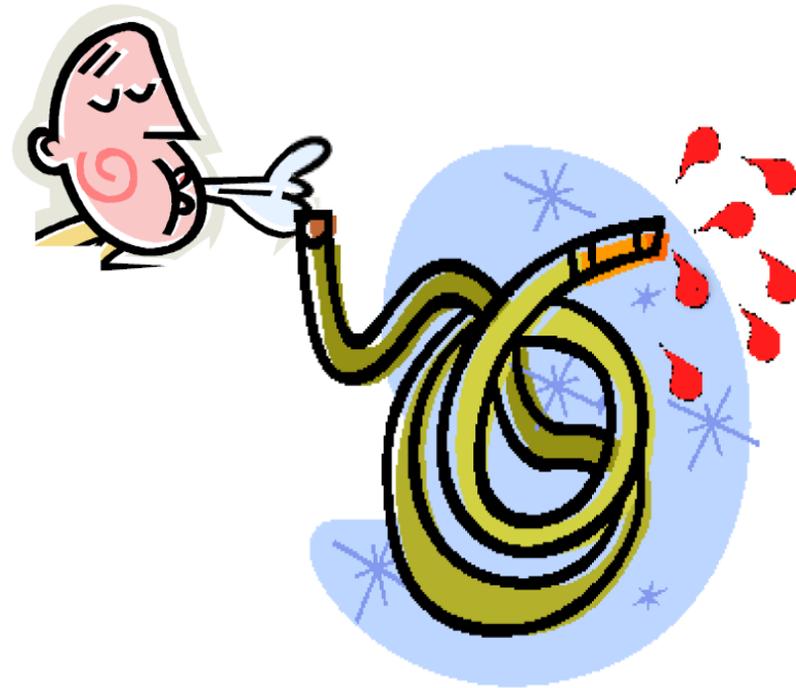
# Hematoma Expansion



# Hematoma growth

- Davis: 218 acute ICH pts scanned within 3 h
  - 73% have some hematoma expansion over the first 24 hours
  - 32% have >33% expansion by 24 h
  - For each 10% ↑ in ICH:
    - 5% ↑ in death
    - 16% ↑ in 1 pt on mRS (worse functional outcome)
- CHANT: 268 acute ICH pts scanned within 6 h
  - 65% had some expansion over 72 h
  - 26% had > 33% expansion by 72 h
  - Expansion > 33% had OR ~4 of worse outcome/death

# BP lowering to prevent ICH growth



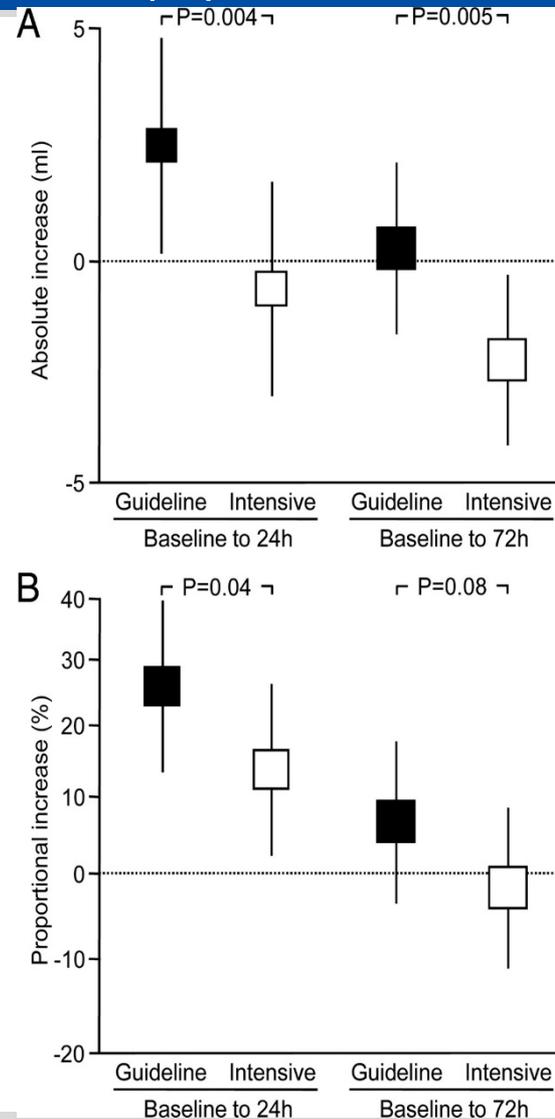
# INTERACT – Phase 1

- Randomized, multicenter, open-label trial of BP lowering
- Treatment within 6 h of onset
- Presenting SBP 150–220 mm Hg
- Randomized to intensive treatment = goal SBP 140  
vs. guideline treatment = goal SBP 180
- CT at baseline, 24 h and 72 h
- Outcomes blinded to treatment

# ICH expansion results

	Guideline (n=172)	Intensive (n=174)	Difference (95% CI)*	p
<b>Haematoma</b>				
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)	..	..
<b>Proportional increase (%)</b>				
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
<b>Absolute increase (mL)</b>				
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

# Effects of early treatment to lower BP on absolute (A) and proportional increase (B) in hematoma volume



Anderson, C. S. et al. Stroke 2010;41:307-312

# INTERACT results

- Early intensive BP control decreased ICH growth
  - Mean growth 36% vs. 14%
  - RRR for substantial growth: 36%
- No adverse events
- No difference in clinical outcomes
  - Study not designed for clinical outcomes
  - Baseline ICH volume not equal in each group

# INTERACT2

- 2839 patients with ICH within 6 hours
- Initial SBP 150-220
- Randomized to goal < 140 or <180
  
- Any agent- open label- but outcomes blinded to treatment

**Table 1. Baseline Characteristics of the Participants.\***

Characteristic	Intensive Blood-Pressure Lowering (N = 1399)	Guideline-Recommended Blood-Pressure Lowering (N = 1430)
Time from onset of ICH to randomization — hr		
Median	3.7	3.7
Interquartile range	2.8–4.8	2.9–4.7
Age — yr	63.0±13.1	64.1±12.6
Male sex — no. (%)	898 (64.2)	882 (61.7)
Recruited from China — no. (%)	947 (67.7)	973 (68.0)
Blood pressure — mm Hg		
Systolic	179±17	179±17
Diastolic	101±15	101±15
NIHSS score <sup>†</sup>		
Median	10	11
Interquartile range	6–15	6–16
GCS score <sup>‡</sup>		
Median	14	14
Interquartile range	12–15	12–15
History of hypertension — no./total no. (%)	1012/1398 (72.4)	1036/1428 (72.5)
Current use of antihypertensive drugs — no./total no. (%)	627/1398 (44.8)	647/1428 (45.3)
Prior intracerebral hemorrhage — no./total no. (%)	115/1398 (8.2)	114/1428 (8.0)
Prior ischemic or undifferentiated stroke — no./total no. (%)	157/1398 (11.2)	166/1428 (11.6)
Prior acute coronary event — no./total no. (%)	39/1398 (2.8)	42/1428 (2.9)
Diabetes mellitus — no./total no. (%)	155/1398 (11.1)	150/1428 (10.5)
Use of warfarin anticoagulation — no./total no. (%)	50/1398 (3.6)	31/1428 (2.2)
Use of aspirin or other antiplatelet agent — no./total no. (%)	123/1398 (8.8)	142/1428 (9.9)
Baseline hematoma volume — ml		
Median	11	11
Interquartile range	6–19	6–20
Deep location of hematoma — no./total no. (%) <sup>§</sup>	1084/1294 (83.8)	1098/1319 (83.2)
Left hemisphere site of hematoma — no./total no. (%)	644/1294 (49.8)	669/1319 (50.7)
Intraventricular extension of hemorrhage — no./total no. (%)	371/1294 (28.7)	369/1319 (28.0)

\* There were no significant differences between the groups in any of the characteristics listed here. ICH denotes intracerebral hemorrhage.

<sup>†</sup> Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (normal neurologic status) to 42 (coma with quadriplegia).

<sup>‡</sup> Scores on the Glasgow Coma Scale (GCS) range from 15 (fully conscious) to 3 (deep coma).

<sup>§</sup> Deep location refers to location in the basal ganglia or thalamus.

**Table 3.** Primary, Secondary, and Safety Outcomes at 90 Days.\*

<b>Variable</b>	<b>Intensive Blood-Pressure Lowering (N=1399)</b>	<b>Guideline- Recommended Blood-Pressure Lowering (N=1430)</b>	<b>Odds Ratio (95% CI)</b>	<b>P Value</b>
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

Anderson CS et al. N Engl J Med. 2013 Jun 20;368(25):2355-65.

**Table 3. Primary, Secondary, and Safety Outcomes at 90 Days.\***

Variable	Intensive Blood-Pressure Lowering (N=1399)	Guideline- Recommended Blood-Pressure Lowering (N=1430)	Odds Ratio (95% CI)	P Value
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)		

**Table 3. Primary, Secondary, and Safety Outcomes at 90 Days.\***

Variable	Intensive Blood-Pressure Lowering (N = 1399)	Guideline- Recommended Blood-Pressure Lowering (N = 1430)	Odds Ratio (95% CI)	P Value
Secondary outcomes				
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

# But didn't decrease ICH growth!!

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

	Blood Pressure Lowering				Absolute (mL) or proportional (%) decrease in intensive group (95% CI)	P Value
	Intensive Group (N = 491)		Guideline Group (N = 473)			
<b>Hematoma volumes</b>						
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 <i>substantial</i> 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.

# BP Variability in INTERACT

A and D: Adjusted for age, sex, and randomized group;

B and E: Adjusted for above plus region, ICH volume at baseline, and high NIHSS scores

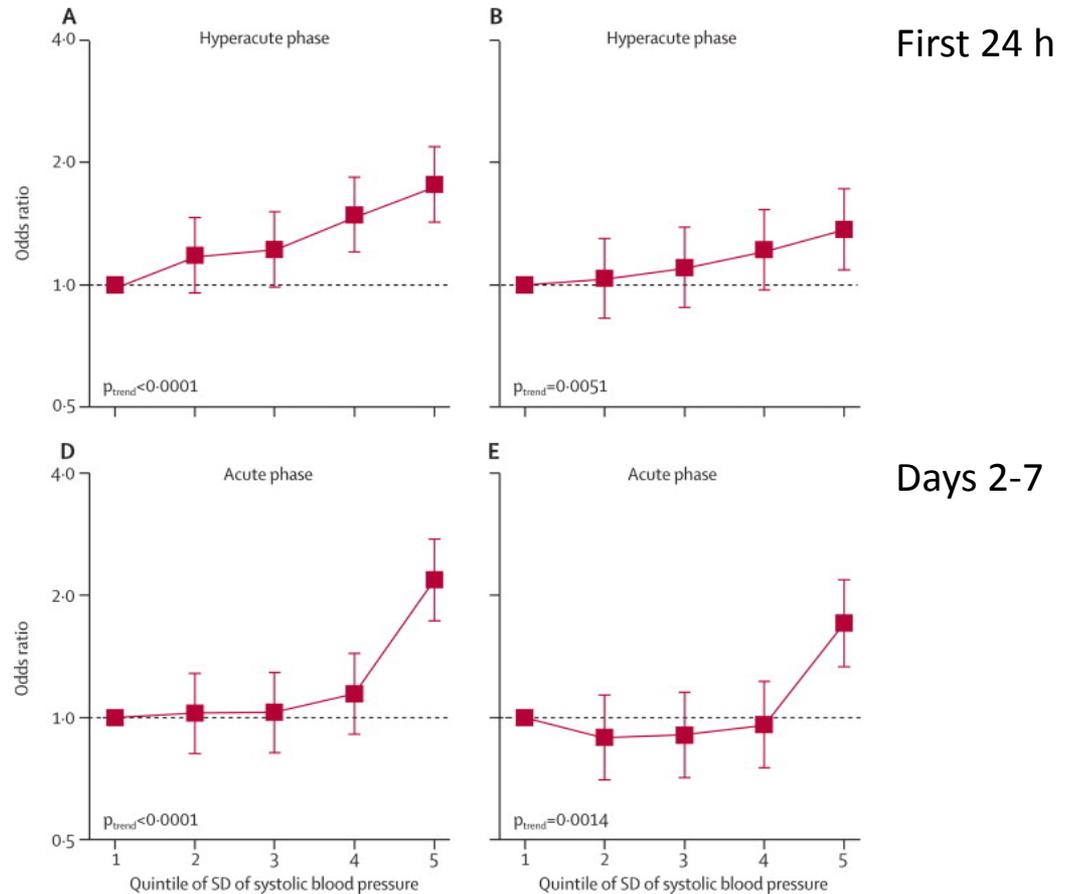
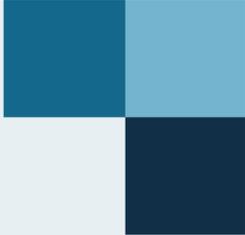
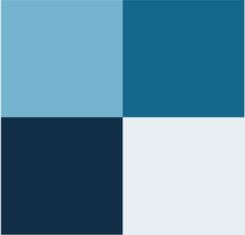


Figure 4 Association between quintiles of SD of systolic blood pressure and death or major disability at 90 days According to models 1–3 for the hyperacute phase (A–C) and models 1–3 for the acute phase (D–F). Lowest quintile is reference.

# INTERACT Conclusions

- Rapid blood pressure lowering to SBP <140 safe
  - For pts presenting 150-220
- Seems to improve broad range of outcomes without significantly reducing ICH expansion
  - How?
  - Benefit seen in % of pts mRS 1
- Perhaps steady BP control in first 24 h more important



# Your poll will show here

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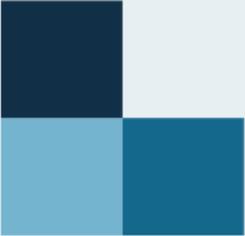
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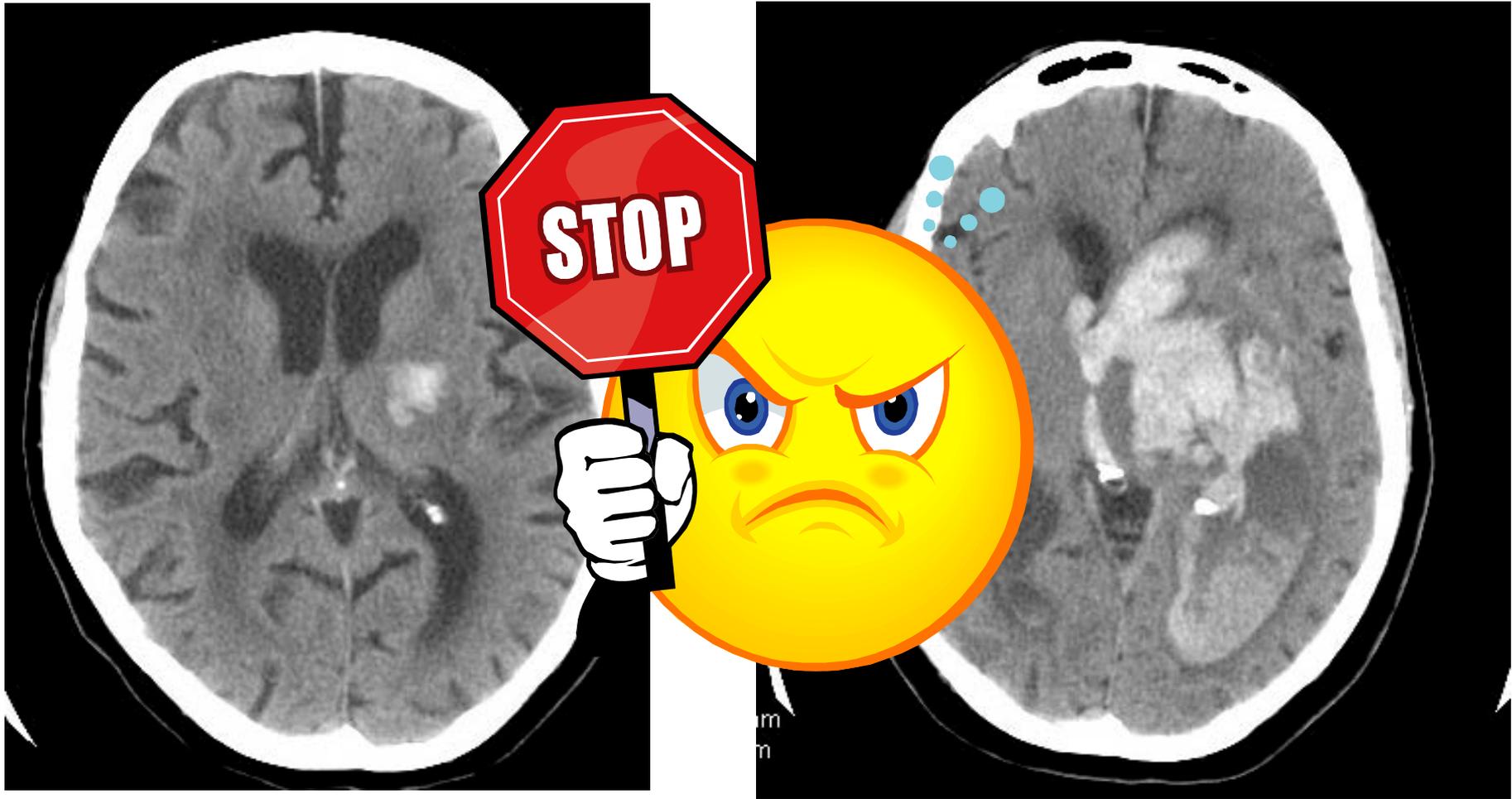
# AHA Guidelines 2015

- For patients with initial SBP 150-220 and without contraindication to BP lowering, SBP treatment to goal 140 mmHg is safe
  - And may improve functional outcome
- For patients with SBP > 220, reasonable to aggressively lower with IV infusions and frequent monitoring
  - No goal given

# Blood pressure- questions

- At this point it is unclear whether aggressive BP reduction reduces ICH growth
  - Trials conflicting
- More aggressive BP control may improve outcomes- how?
- Target unknown!
- Awaiting results of ATACH2
  - Does absolute BP target matter?
- Does the medication class used matter?
  
- Patients with acute ICH and SBP > 220, ↓ lower 25% over 1 h (230 → 170) and then to 150 over the next few hours
  - Indications/contraindications on a case-by-case basis

# Hematoma Expansion

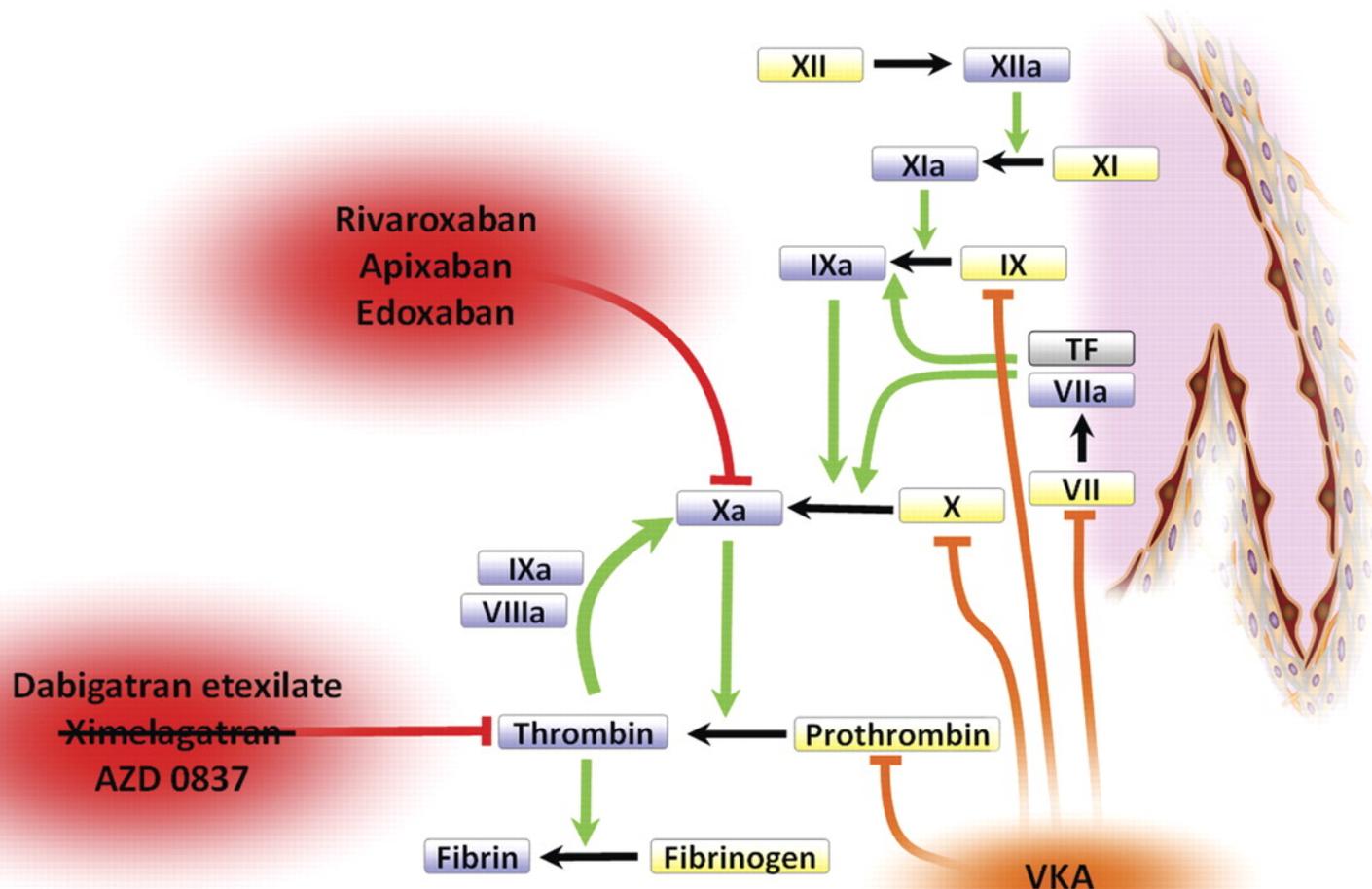


# Warfarin-associated ICH

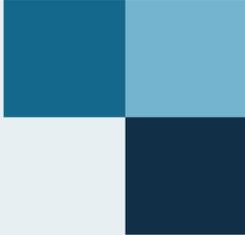
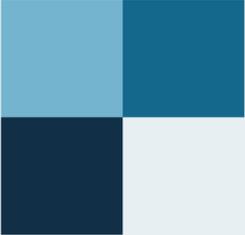
- ICH volume 2x greater in patients with OAT ICH
- Hemorrhage expansion (defined as >33% increase in ICH volume) 2x more common
  - 56% of patients with OAT ICH vs. 26% of SICH,  $p=0.006$
- Mortality was substantially higher in OAT ICH
  - 62% versus 17%,  $p<0.001$
- ICH in an anticoagulated patient is likely the most critical neuro emergency you will see
  - Act quickly, watch the patient carefully, get them to NICU!

Cucchiara et al. Stroke. 2008 Nov;39(11):2993-6.

# The coagulation cascade.



Steffel J , and Braunwald E Eur Heart J  
2011;eurheartj.ehr052



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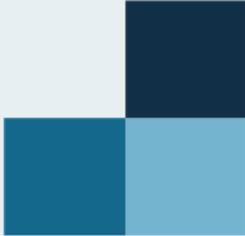
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# Reversal of Warfarin

- Agents used for reversal
  - Fresh frozen plasma (FFP)
  - Vitamin K
  - Recombinant factor VIIa
  - Prothrombin complex concentrates (PCC)
- Issues to consider
  - FFP carries viral risk, half-life is only 8-12 h
  - PCC factor concentrations vary by batch/manufacturer
  - PCC and rFVIIa have smaller volumes and more rapid administration than FFP
  - Vitamin K needed in addition to others

**Ansell J, et al. *Chest*. 2001;119(suppl 1):22S-38S; Hanley JP. *J Clin Pathol*. 2004;57:1132-1139; Baker RI, et al. *Med J Aust*. 2004;181:492-497; Mayer SA, Rincon F. *Lancet Neurol*. 2005;4:662-672; Manno EM, et al. *Mayo Clin Proc*. 2005;80:420-426; Steiner T, et al. *Stroke*. 2006;37:256-262; Freeman WD, et al. *Mayo Clin Proc*. 2004;79:1495-1500; Huttner HB, et al. *Stroke*. 2006;37:1465-1470.**

# Vitamin K

- Factors II, VII, IX, X, proteins C and S!
- IV → reversal of INR beginning 4-6 hours
  - PREFERRED ROUTE- 10 mg IV over 10 min
    - Risk? Anaphylaxis (very rare- don't let it stop you!)
- Subcutaneous → variable absorption- reversal beginning 8-12 h
- Oral- better than subQ (second choice)
  
- Reversal of warfarin is persistent!

# Prothrombin Complex Concentrates

- Different formulations- newest approved (Kcentra) has inactivated forms of coagulation Factors II, VII, IX and X, and antithrombotic Proteins C and S

Pre-treatment INR	2 – < 4	4 – 6	> 6
Dose* of Kcentra (units† of Factor IX) / kg body weight	25	35	50
Maximum dose‡ (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

# Prothrombin complex concentrates versus fresh frozen plasma

	<b>PCC</b>	<b>FFP</b>
Blood type matching required	No	Yes
Thawing time	None	30–45 min/unit
Infection risk	Yes	Yes
Thrombosis risk	Yes	Yes
Clotting factor concentration	High	Low
Infusion volume	Less than 200 ml	1,000–3,000 ml
Speed of INR correction	Quicker *(20-45min)	Slower (hours)
Availability	Now Available!	Available
Expensive	Yes	Moderate
Duration	unclear	6-8 hrs!!

Bershad and Suarez. Neurocritical Care, 2010: 12 (3), 403-413

# What should you do?

- Warfarin → Vitamin K 10 mg IV STAT over 10 min
- Plus PCCs or FFP
- If no PCCs avail-> FFP 10-20 ml/kg (4-6 units for average pts) STAT
  - May need lasix between doses- volume 1-1.5 L
- Recheck INR q6 hrs- redose FFP as needed (not PCC's)
- Goal INR <1.4
  - Need 2 consecutive nl INR' s before you can stop checking q6!
- Close neuro checks!! All pts to Neuro-ICU!
- Repeat HCT in 6 h, sooner if any change in exam

# Newer oral anticoagulants

- Dabigatran- direct thrombin inhibitor
- **Idarucizumab- Praxbind- approved last week by FDA**
- Rivaroxaban, apixaban, edoxaban- factor Xa inhibitors
  - Overall, short half-lives (5-15 hours)
  - Vitamin K not useful
  - Consult with hematologist useful
- If taken within 2 hours, consider activated charcoal
- Preliminary data suggests PCCs reverse rivaroxaban and apixaban
  - Provide thrombin downstream of factor Xa
  - Directed antidotes for FXa inhibitors in clinical trials
  - Andexanet- - trial started, will also get accelerated review

Pollack CV et al. Idarucizumab for dabigatran reversal; N Engl J Med 2015.

# Surgical Evacuation

- Cerebellar hemorrhage  $>3$  cm w/ neurological deterioration or brain stem compression and ventricular obstruction



- Structural lesion if chance for good outcome and lesion surgically accessible
- What about everyone else?

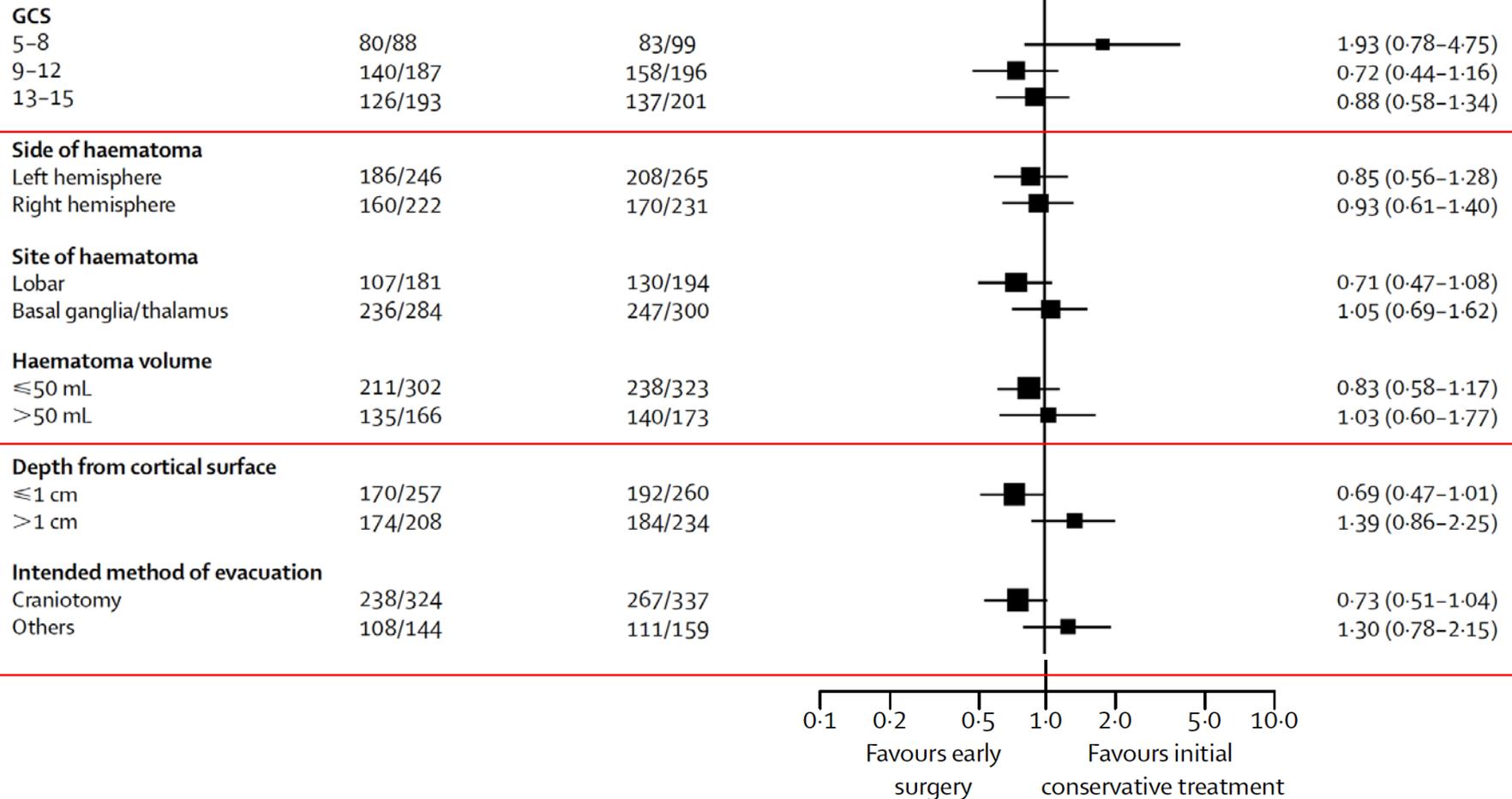
# Surgical Trial for ICH (STICH)

- 1033 patients enrolled from > 20 countries
  - Nearly double the total # pts enrolled (561) in all prior trials combined
- Early surgical evacuation vs. medical therapy
  - 25% of medical group declined and had late surgery
- Enrollment based on surgeon being “uncertain about the benefits of either treatment”
- Patients with GCS  $\geq 5$
- Outcome determined by prognosis based GOS (taking into account age, admission GCS, and ICH volume)
- Surgery mostly by craniotomy

**NO OVERALL DIFFERENCE**

Mendelow AD, Lancet 2005; 365: 387-97.

# Prespecified Subgroup Analysis



# STICH2

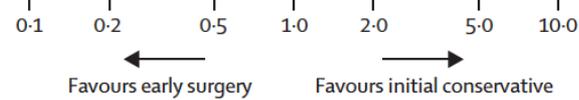
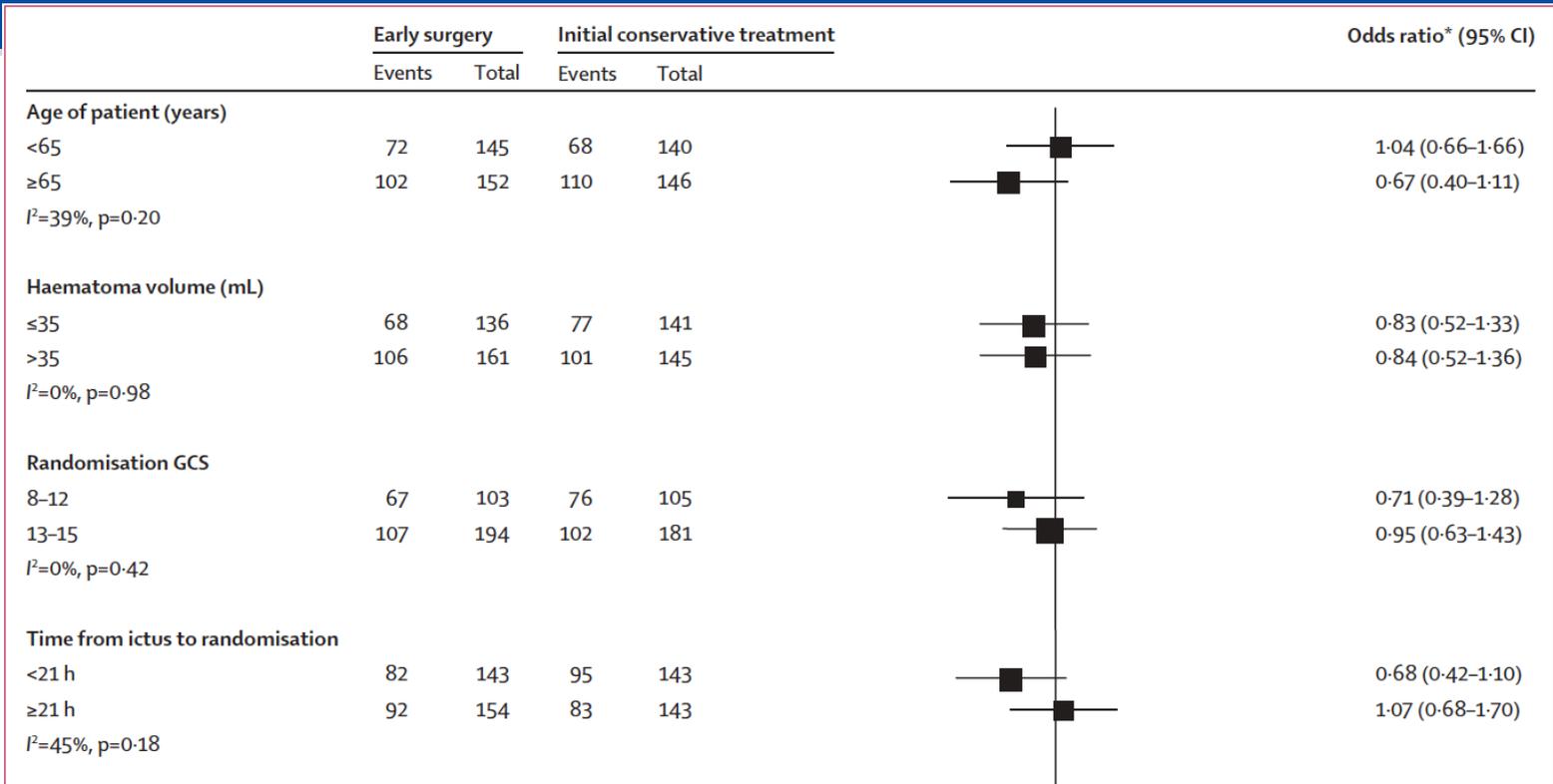
- 601 patients randomized to early surgery vs. early conservative management
- GCS > 8
- Supratentorial ICH, 10-100 mL
- within 48 h of onset
- $\leq 1$  cm of cortex
- Craniotomy

# STICH 2 Results

	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%)	..	..
Secondary outcomes	298	291		
Mortality at 6 months			0.095*	5.6% (-1.0 to 12.2)
Dead	54 (18%)	69 (24%)	..	..
Alive	244 (82%)	222 (76%)	..	..
Rankin			0.128*; 0.147†	..
0	20 (7%)	16 (6%)	..	..
1	54 (18%)	57 (20%)	..	..
2	58 (20%)	41 (14%)	..	..
3	35 (12%)	32 (11%)	..	..
4	40 (14%)	28 (10%)	..	..
5	34 (12%)	41 (14%)	..	..
Dead	54 (18%)	69 (24%)	..	..
EuroQoL Index	235	210	0.751‡	..
Median (IQR; range)	0.64 (0.20 to 0.85; -0.59 to 1.00)	0.69 (0.08 to 0.82; -0.59 to 1.00)	..	..

Data are number or number (%), unless otherwise indicated. EuroQol utility index was calculated with UK weightings provided by the EuroQol Group Foundation. Absolute differences (95% CIs) are provided for binary outcomes. Rankin was not available for three patients in the early surgery group and for seven in the initial conservative group. GOSE was not available for one patient in the early surgery group and five patients in the initial conservative group. GOSE=Extended Glasgow Outcome Scale. \* $\chi^2$  test. †Proportional odds model. ‡Mann-Whitney test.

**Table 4: Prespecified outcomes at 6 months**



# AHA Guidelines on surgery

- Cerebellar ICH with neurological deterioration and/or hydrocephalus should have surgical evacuation as soon as possible
- For most other patients, no clear benefit of surgical evacuation
  - Watch and wait approach
- Supratentorial evacuation in deteriorating patients might be considered as a life-saving measure
- Decompressive craniectomy +/- ICH evacuation might reduce mortality for comatose patients with midline shift or refractory ICP elevations

# Prevent Complications



# Seizures and ICH

- Seizures are more frequent in ICH than in ischemic stroke
- Seizure risk 8% after ICH
- Most seizures at onset or  $\leq 24$  h of ICH
- More commonly associated with lobar than deep ICH
- Poorer outcomes
  - Neuronal injury and destabilization of critically ill patient
  - Nonconvulsive seizures may contribute to coma
  - Seizures associated with deterioration of NIHSS and increase in midline shift

Vespa PM, et al. *Neurology*. 2003;60:1441-1446; Mayer SA, Rincon F. *Lancet Neurol*. 2005;4:662-672; Passero S, et al. *Epilepsia*. 2002;43:1175-1180; Qureshi AI, et al. *NEJM*. 2001;344:1450-1460; Broderick JP, et al. *Stroke*. 1999;30:905-915.

# Management of Seizures

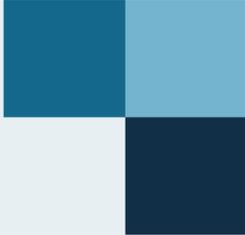
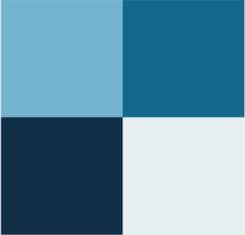
- Use anticonvulsants for seizure at onset of ICH or witnessed seizures in hospital
- Monitor patients who aren't waking up for subclinical seizures
  - Bedside routine EEG if pt unresponsive
  - Continuous if patient fluctuating

# Prophylactic AEDs?

- AHA 2015: Prophylactic AEDs should not be used.
  - Based on 2 studies showing higher mortality in patients treated prophylactically with AEDs (primarily phenytoin)
  - Also don't seem to prevent lesion-related epilepsy

# Supportive Measures

- Intubation
  - Airway protection
  - ICP management
- Aspiration prevention
  - Dysphagia screening for all patients before po intake
- Ventriculostomy placement
  - IVH, hydrocephalus, elevated ICP
- Normothermia – duration of fever an independent predictor of death
- Normoglycemia



# Your poll will show here

1

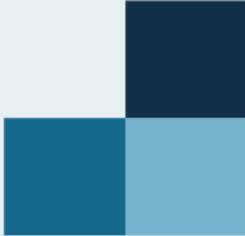
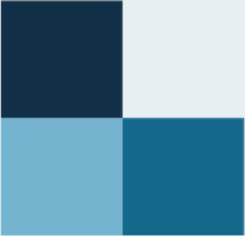
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# DVT Prevention

- DVT prophylaxis
  - SCDs better than just stockings
    - DVT at day 10 (by U/S) in 4.7% vs 15.9%
  - SC heparin safe and effective beginning at 48 hrs
    - Trial of SQH starting on day 10, 4 or 2
    - Fewer PE's and DVTs in earlier group
    - No difference in rebleeding
- START SCDs (pneumatic compression dressings) on admission
- START SC prophylactic heparin or LMWH once ICH size is stable in immobile patients after 1-4 days from onset

Lacut, Neurology, 2005. Boer, JNNP, 1991.

AHA guidelines 2015.

# Prevent Recurrent ICH

- Long-term BP Control!
- 1145 patients who survived at least 90 days after ICH
- Blood pressure measurements at 3, 6, 9, and 12 months, and then every 6 months
  
- Inadequate BP control was associated with higher risk of
  - lobar ICH (HR 3.53 [95% CI, 1.65-7.54])
  - nonlobar ICH (HR 4.23 [95% CI, 1.02-17.52])

Biffi et al. JAMA. 2015 Sep 1;314(9):904-12

# Research



- Minimally invasive surgery versus best medical management

- And many other preclinical, phase II, and population-based studies that will lead to our next treatment advances!

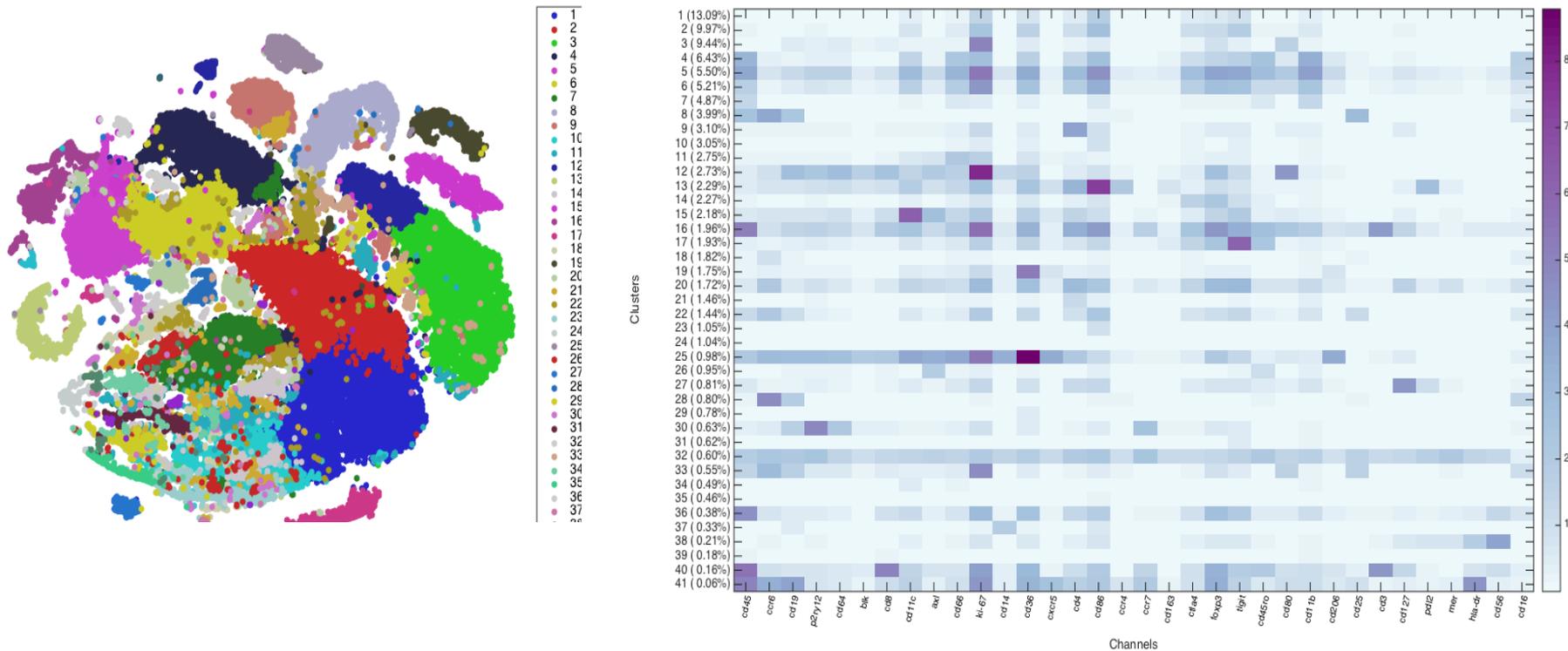


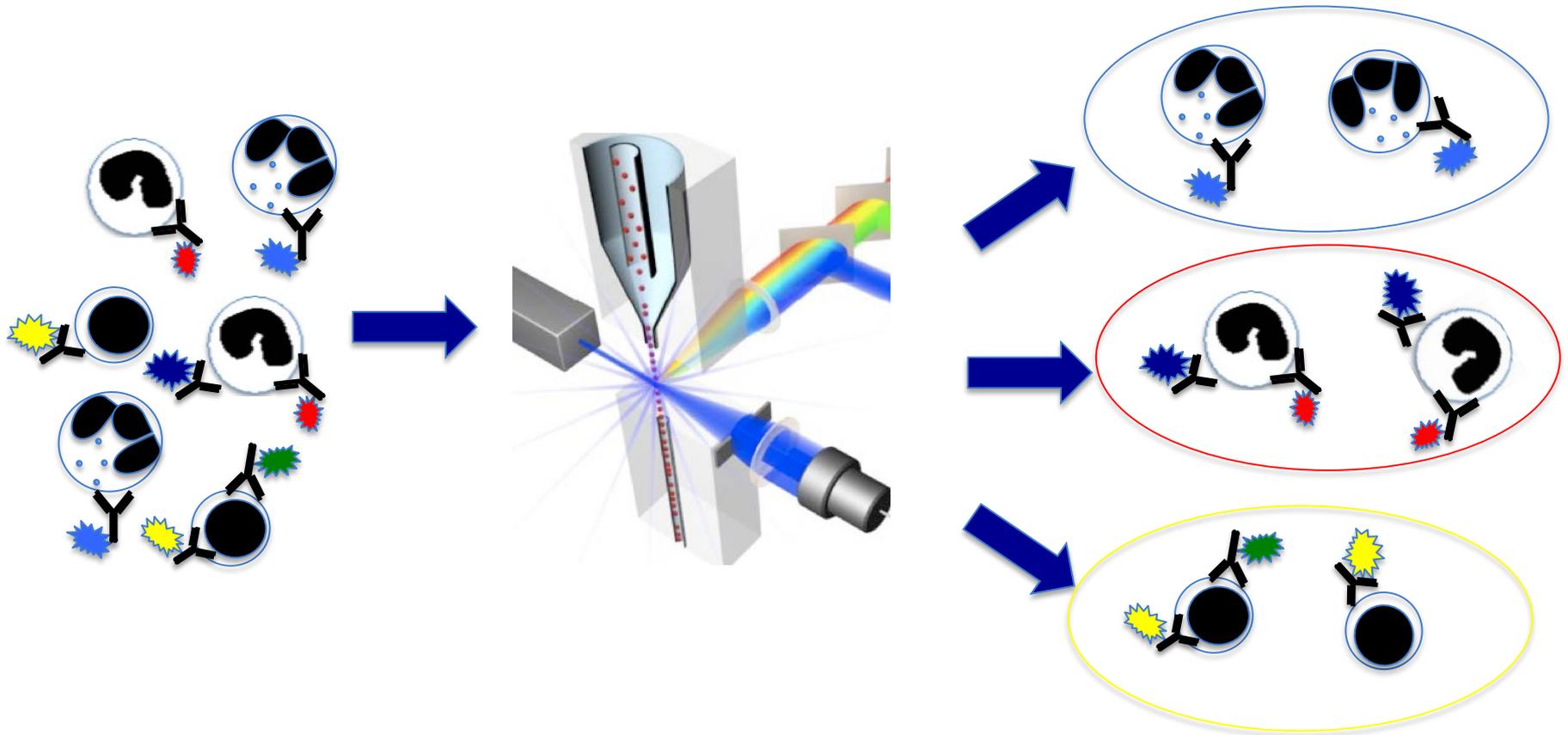
- Deferoxamine versus placebo
  - Iron-chelating agent
  - Anti-inflammatory
  - Potential neuroprotectant



Discovering the cellular immune responses in living ICH patients over time.

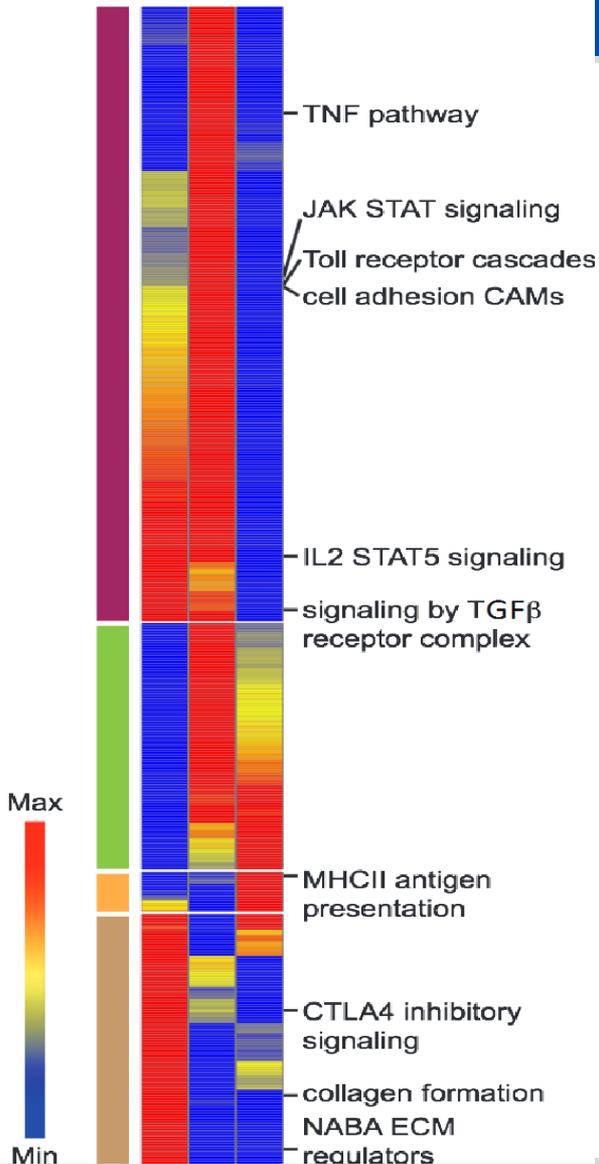
# CyTOF identifies 41 cells populations in the brain





Each population has entire transcriptome profiled by RNAseq

Cluster ID  
 ICH055-100 h  
 ICH111-50 h  
 ICH095-24 h



# The Future of ICH Management

- ICH remains with high morbidity and mortality
- Advances in our understanding of disease
  - And in what doesn't help improve outcomes
- Major questions on management remain
- Embrace research! Our next management approaches will be defined by ongoing trials and preclinical work.

# Thanks!

Happy to answer questions!