Management of ICH in the ICU

KYLE HOBBS, MD
STANFORD STROKE CENTER
DEPARTMENT OF NEUROCRITICAL CARE AND STROKE

Terminology

- Intracranial hemorrhage: Any hemorrhage within cranial vault
  - Epidural, subdural, SAH, intraventricular, parenchymal
- Intracerebral hemorrhage: Bleeding in the brain parenchyma

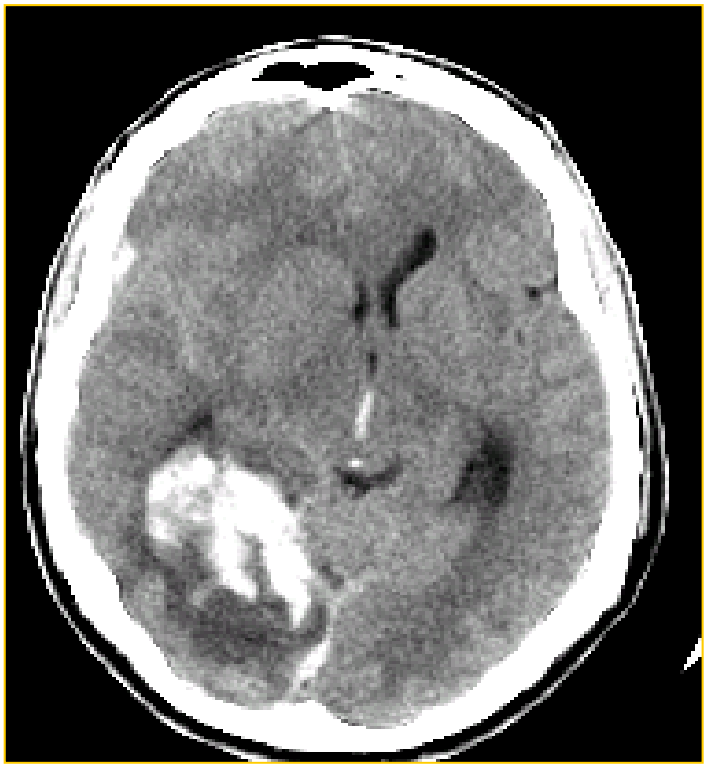
Epidural Hematoma

Subdural Hematoma

Subarachnoid Hemorrhage

Intracerebral Hemorrhage

- The numbers
- Current status
- Recent updates
- The future



A Case

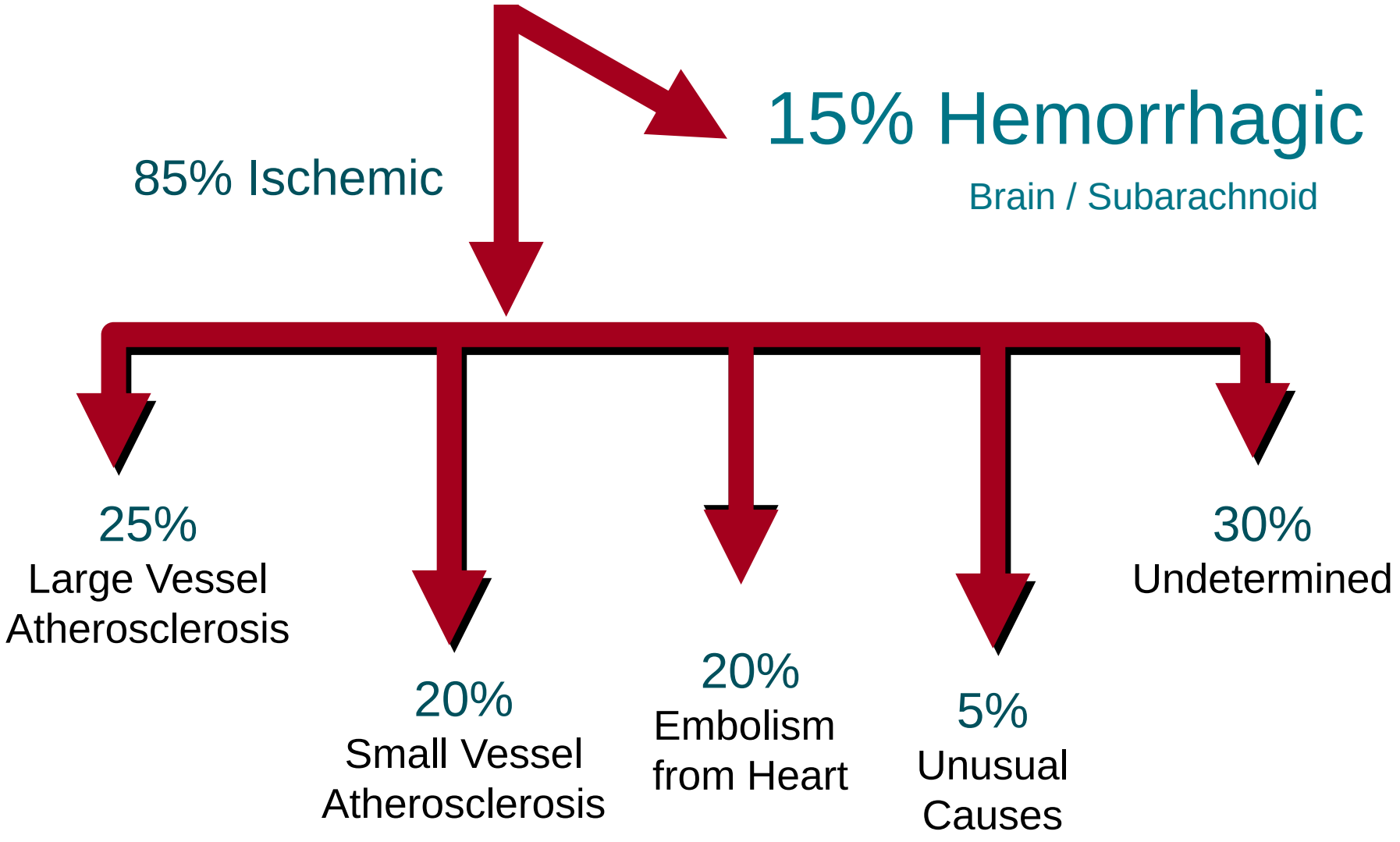
ID: 55year old male

CC: Sudden onset left-sided weakness and headache, progressive obtundation

Past Medical History:

Hypertension

Stroke

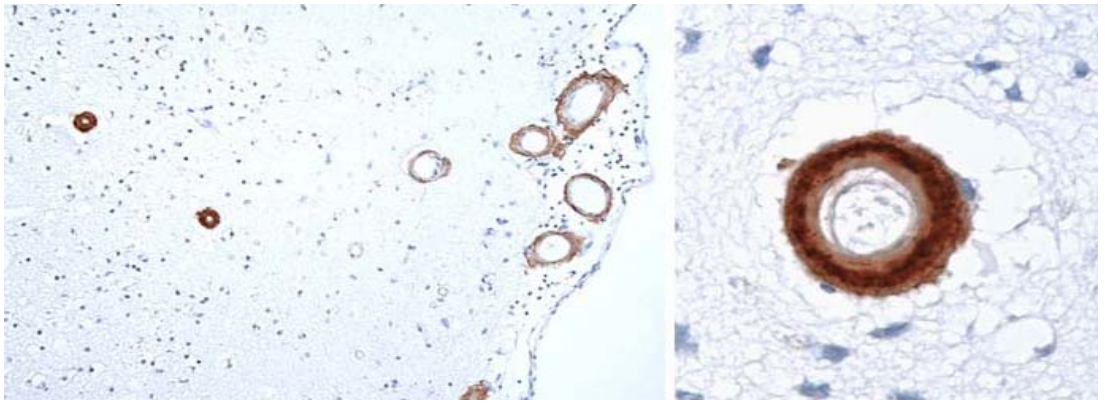

85% Ischemic
15% Hemorrhagic
Brain / Subarachnoid
25%
Large Vessel
Atherosclerosis
20%
Small Vessel
Atherosclerosis
20%
Embolism
from Heart
5%
Unusual
Causes
30%
Undetermined

By the numbers…

- 37,000 - 63,000 each year in the U.S.
- >20% patients experience decrease in Glasgow Coma Scale (GCS) by ≥2 points between EMS and ED evaluation
- Mortality 35-50% at 3 months
- Only 20% independent at 6 months
- $36.5 Billion – cost of stroke annually, including health care services, medications, missed work/lost productivity

Types of Spontaneous (Non-traumatic) Intracerebral Hemorrhage

- Primary (80-90%)
  - Hypertension
  - Cerebral amyloid angiopathy
- Secondary
  - Coagulopathy
  - Ischemic stroke
  - Vascular malformation
  - Tumors
  - Hypertensive encephalopathy/ PRES
  - Re-perfusion injury
  - Vasculopathy
  - Endocarditis/ Infection



Campbell DM et al. J Neurol. 2008

Pathogenesis of Primary Intracerebral Hemorrhage

1. Spontaneous rupture of small penetrating artery due to changes in the vessel wall leading to direct tissue destruction
2. Hematoma expansion
3. Edema and secondary neuronal injury in peri-hematomal region surrounding the hematoma
4. Mass effect and further injury; Inflammation

Management of ICH

- ABCs
- Obtain imaging (diagnosis)
- Severity Score
- Management in an ICU

- Management:
- Reverse coagulopathy
- Blood pressure management
- Surgery

Grading of Intracerebral Hemorrhage

- Glasgow Coma Scale

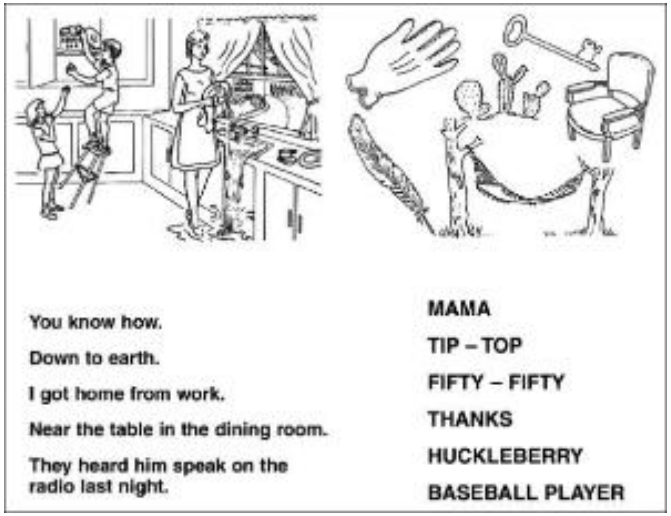
Glasgow Coma Scale

Best eye response (E)	Spontaneous – open with blinking at baseline	4
	Opens to verbal command, speech, or shout	3
	Opens to pain, not applied to face	2
	None	1
Best verbal response (V)	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate responses, words discernible	3
	Incomprehensible speech	2
	None	1
Best motor response (M)	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws from pain	4
	Abnormal (spastic) flexion, decorticate posture	3
	Extensor (rigid) response, decerebrate posture	2
	None	1

- NIH Stroke Scale

1. **Level of consciousness**
   0 alert
   1 drowsy
   2 stuporous
   3 coma
2. **LOC questions (month, age)**
   0 both correct
   1 one correct
   2 incorrect
3. **LOC commands (close eyes, make a fist)**
   0 both correct
   1 one correct
   2 incorrect
4. **Best gaze**
   0 normal
   1 partial gaze palsy
   2 forced deviation
5. **Visual fields**
   0 no visual loss
   1 partial hemi
   2 complete hemi
   3 bilateral hemi
6. **Facial palsy**
   0 normal
   1 minor
   2 partial
   3 complete

7-10. **Motor (L/R arm + leg)**
   0 no drift
   1 drift
   2 can't resist gravity
   3 no effort against gravity
   4 no movement
   UN amputation/joint fusion
11. **Limb ataxia (Finger-Nose, Heel-Knee-Shin)**
   0 absent
   1 present in 1 limb
   2 present in 2 limbs
12. **Sensation (pinprick)**
   0 normal
   1 partial loss
   2 severe loss
13. **Best language**
   0 no aphasia
   1 mild-mod aphasia
   2 severe aphasia
   3 mute
14. **Dysarthria**
   0 none
   1 mild-mod
   2 near to unintelligible or worse
   UN intubated/barrier
15. **Extinction and inattention**
   0 no neglect
   1 partial neglect
   2 complete neglect

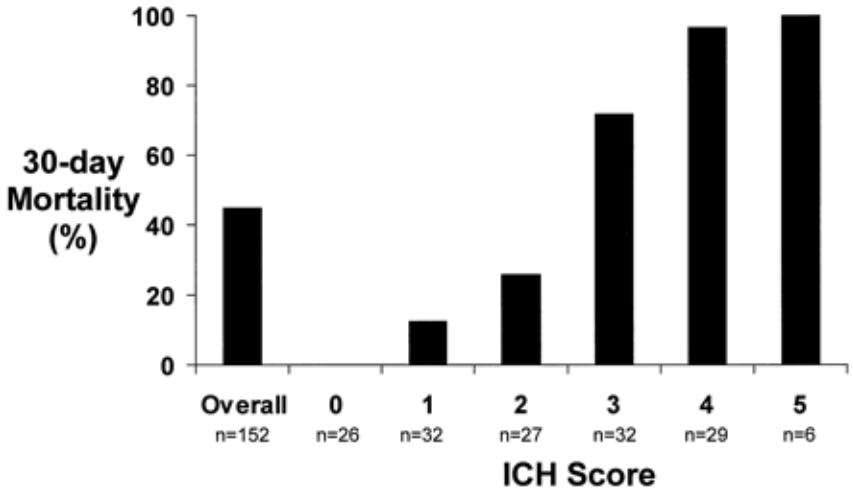


Grading of Intracerebral Hemorrhage

- ICH Score

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 JC, et al. *Stroke* 2001.

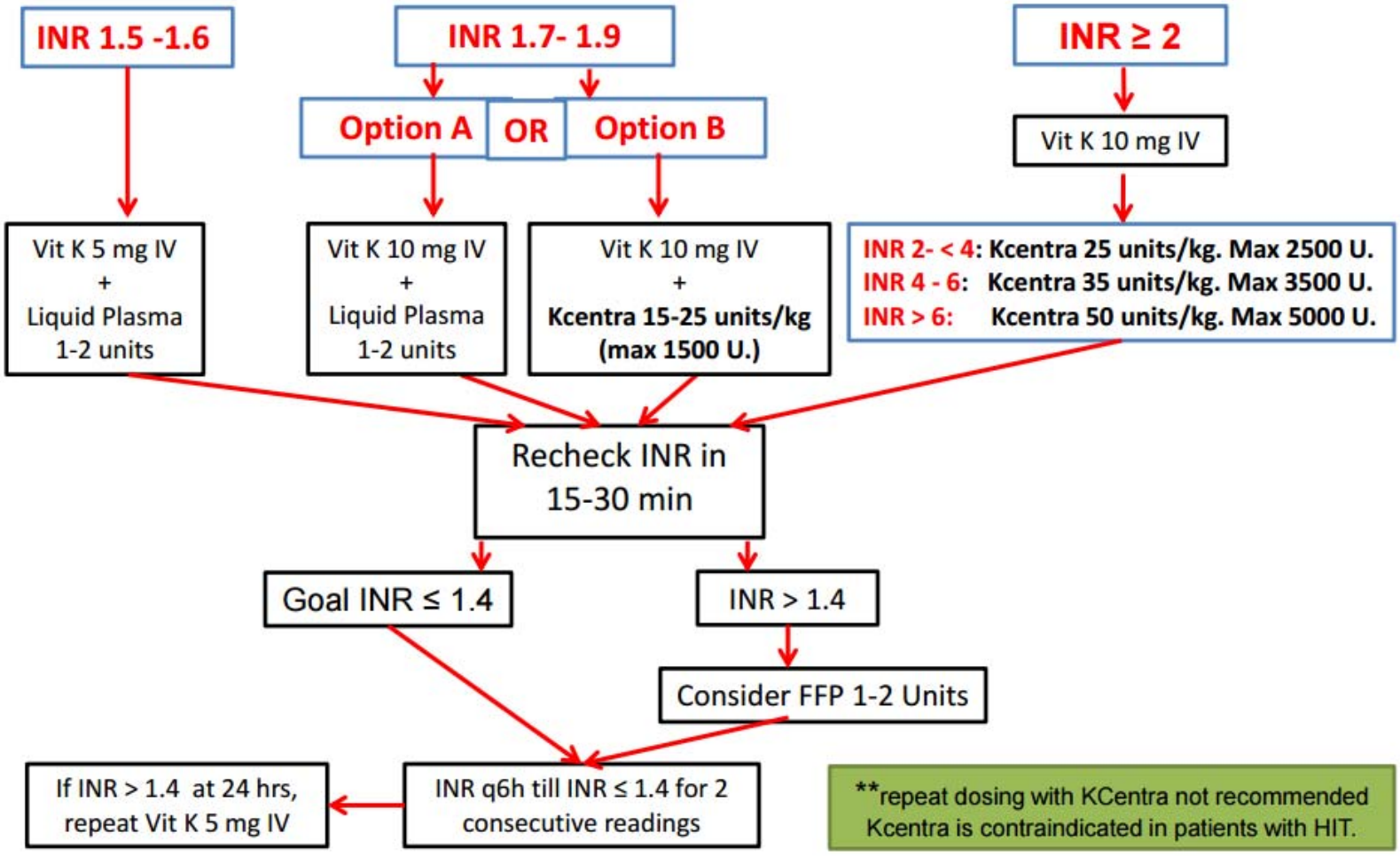
Reversal of Coagulopathy

- Increased risk of ICH and ICH expansion with underlying hemostatic abnormalities
  - Oral anticoagulants
  - Antiplatelet agents
  - Inherited coagulation factor deficiencies
  - Inherited or acquired platelet deficiencies

Reversal of Coagulopathy

- Oral anticoagulants
  - Vitamin K antagonist – Warfarin
  - Novel Oral Anticoagulants (NOACs)
    - Direct thrombin inhibitor – Dabigatran
    - Factor Xa inhibitors – Apixaban, Rivaroxaban

Stanford emergency warfarin reversal protocol



6/23/2015

Reversal of Coagulopathy

- Reversal of NOACs (dabigatran, apixaban, rivaroxaban)
  - No randomized trials regarding reversal of these agents
  - ½ lives range from 5-15 hours
  - Activated charcoal can be considered if recently taken
  - Recommended to give 4-factor PCC if factor Xa inhibitor ingested within 3-5 half lives of drug
  - Dialysis for dabigatran

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

ABSTRACT

BACKGROUND

Specific reversal agents for non–vitamin K antagonist oral anticoagulants are lacking. Idarucizumab, an antibody fragment, was developed to reverse the anticoagulant effects of dabigatran.

METHODS

We undertook this prospective cohort study to determine the safety of 5 g of intravenous idarucizumab and its capacity to reverse the anticoagulant effects of dabigatran in patients who had serious bleeding (group A) or required an urgent procedure (group B). The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab, on the basis of the determination at a central laboratory of the dilute thrombin time or ecarin clotting time. A key secondary end point was the restoration of hemostasis.

RESULTS

This interim analysis included 90 patients who received idarucizumab (51 patients in group A and 39 in group B). Among 68 patients with an elevated dilute thrombin time and 81 with an elevated ecarin clotting time at baseline, the median maximum percentage reversal was 100% (95% confidence interval, 100 to 100). Idarucizumab normalized the test results in 88 to 98% of the patients, an effect that was evident within minutes. Concentrations of unbound dabigatran remained below 20 ng per milliliter at 24 hours in 79% of the patients. Among 35 patients in group A who could be assessed, hemostasis, as determined by local investigators, was restored at a median of 11.4 hours. Among 36 patients in group B who underwent a procedure, normal intraoperative hemostasis was reported in 33, and mildly or moderately abnormal hemostasis was reported in 2 patients and 1 patient, respectively. One thrombotic event occurred within 72 hours after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated.

CONCLUSIONS

Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes. (Funded by Boehringer Ingelheim; RE-VERSE AD ClinicalTrials.gov number, NCT02104947.)

Stanford University

Reversal of Coagulopathy

- Studies examining effect of antiplatelet medication on ICH growth conflicting
- Reasonable to give platelets if patient taking antiplatelet agent
  - PATCH trial ongoing
- If thrombocytopenic, will often transfuse with platelet goal > 100K

Blood Pressure in ICH

Why does it matter?

- Elevated BP very common after acute ICH
  - Pre-existing HTN
  - Stress/Pain
  - Elevated ICP

- Elevated BP associated with:
  - Hematoma expansion
  - Neurologic deterioration
  - Poorer outcomes

Ligh C et al, 2005

INTERACT 2

- Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2
- May 2013
- SBP < 140 vs. SBP < 180
- No difference in death or major disability (p=0.06)
- Functional benefit in intensive treatment arm (ordinal mRS, quality-of-life)
- Study criticisms

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
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 CS, et al, NEJM, 2013.

Blood Pressure in ICH

Current AHA/ASA Guidelines (2015):

- For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe (Class 1; Level of Evidence A) and can be effective for improving functional outcome (Class Iia; Level of Evidence B).

- For ICH patients presenting with SBP >220 mm Hg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring (Class IIb; Level of Evidence C).

Hemphill et al. Stroke. 2015.

Blood Pressure in ICH

The controversy continues…

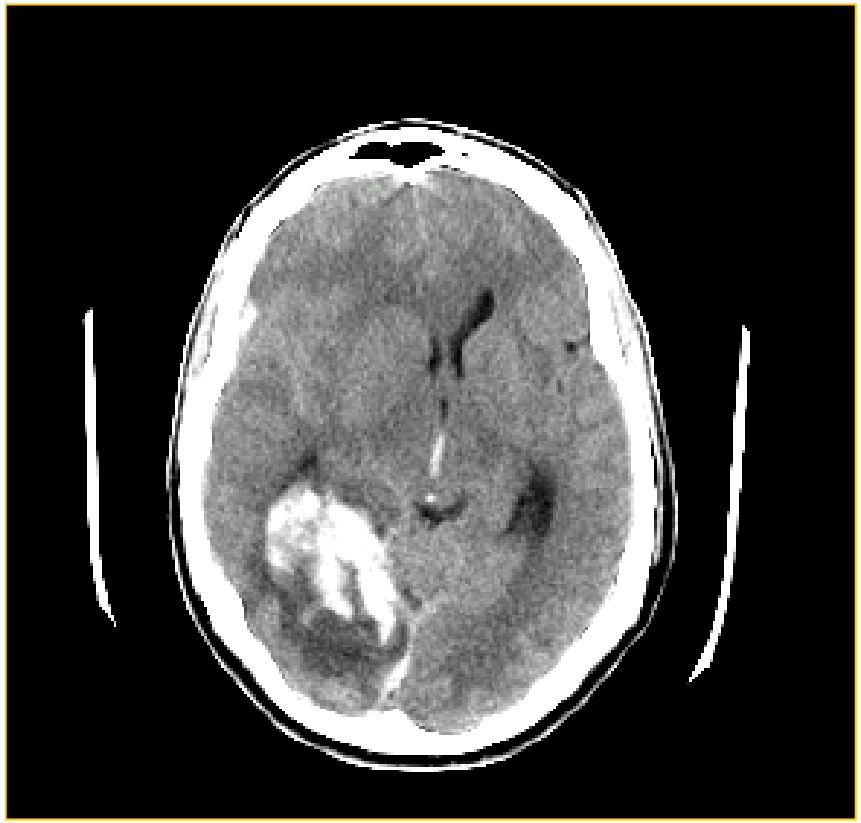
- ATACH II trial recently stopped for futility
  - Also randomized to SBP < 140 vs < 180
- Important to individualize your management
  - If concern for elevated ICP, maintain CPP > 60

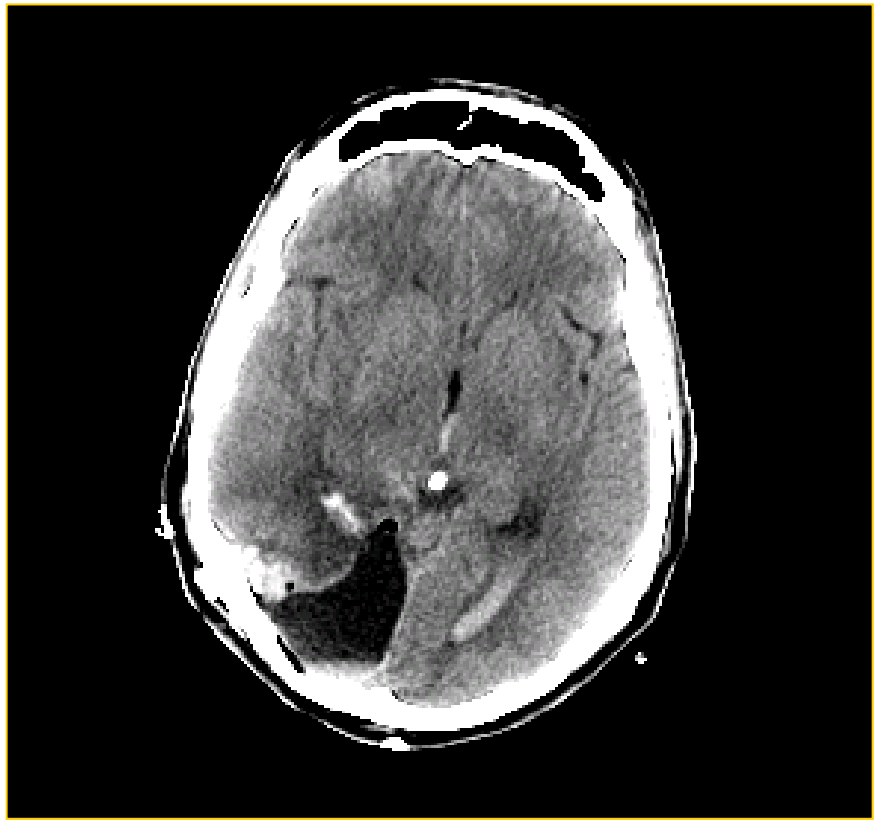
$$CPP = MAP - ICP$$

ICP Monitoring After ICH

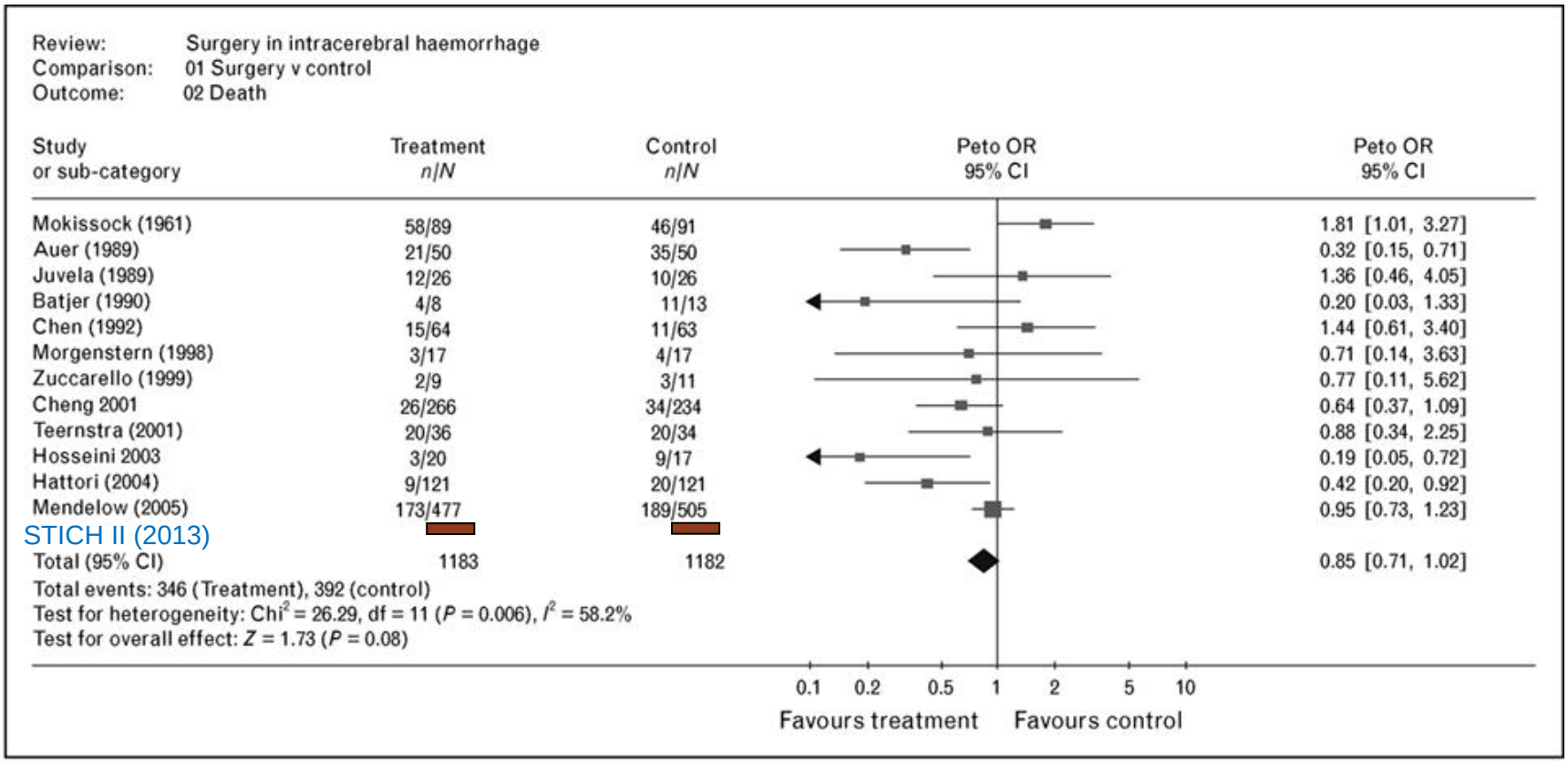
- If patient has hydrocephalus, ventricular drainage is indicated
- If GCS $\leq$ 8, or if signs of transtentorial herniation, consider EVD/ICP monitoring
  - Maintain CPP 50-70
- No role for corticosteroids in elevated ICP due to ICH

Surgery for ICH





Surgery for ICH



Data from [3••,6,13,15,16••,17,18].

Why do surgical ICH trials fail??

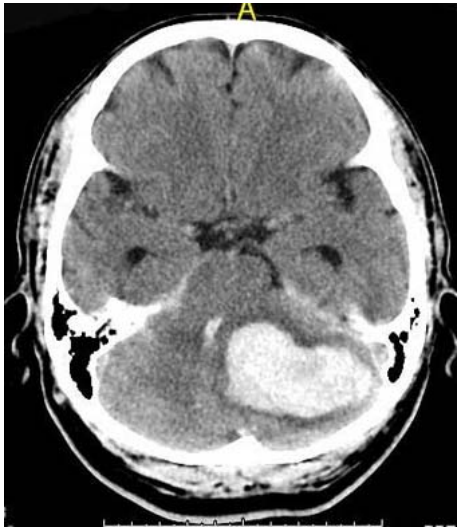
Mendelow and Unterberg, Curr Opinion Critical Care, 2007.

Surgical Treatment of Posterior Fossa Hemorrhage

- Posterior fossa hemorrhage has higher risk of rapid deterioration due to smaller confined space

- Cerebellar hemorrhage and subsequent edema can cause obstructive hydrocephalus or local brainstem compression
  - Non-randomized studies suggest surgical decompression if:
    - Cerebellar hemorrhage is >3cm in diameter
    - Brainstem compression
    - Obstructive hydrocephalus

- Management with EVD alone is insufficient

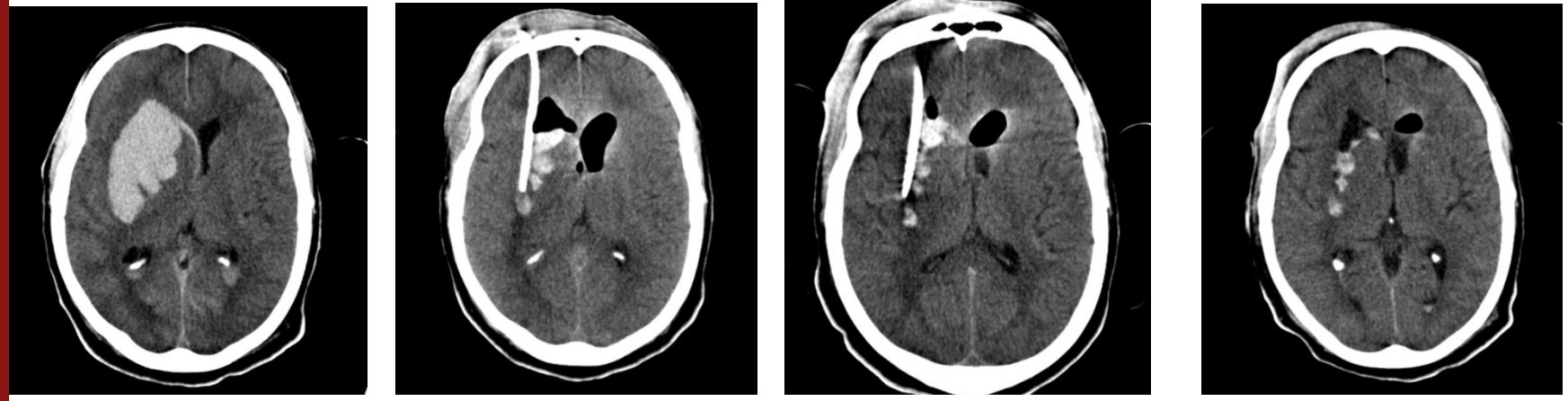


Minimally Invasive Approaches

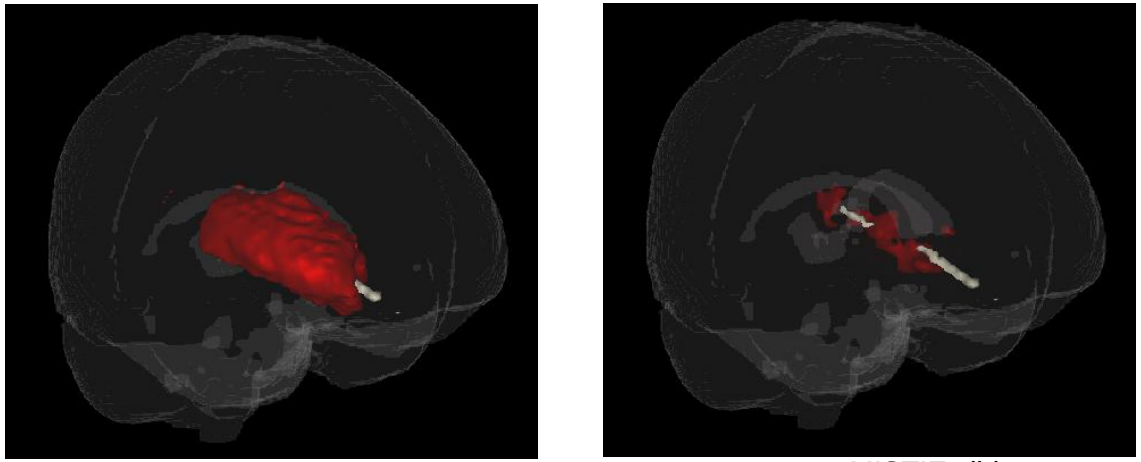
Catheter plus tPA?

Post-Surgery

Pre-surgery | +20 Hr. | +42 Hr. | +52 Hrs.



3D post-op & post rt-PA



MISTIE slides courtesy of Dan Hanley, JHU, from ISC 2013.

MISTIE II

(Minimally Invasive Surgery plus tPA for Intracranial Hemorrhage Evacuation)

Key I/E Criteria

Inclusion

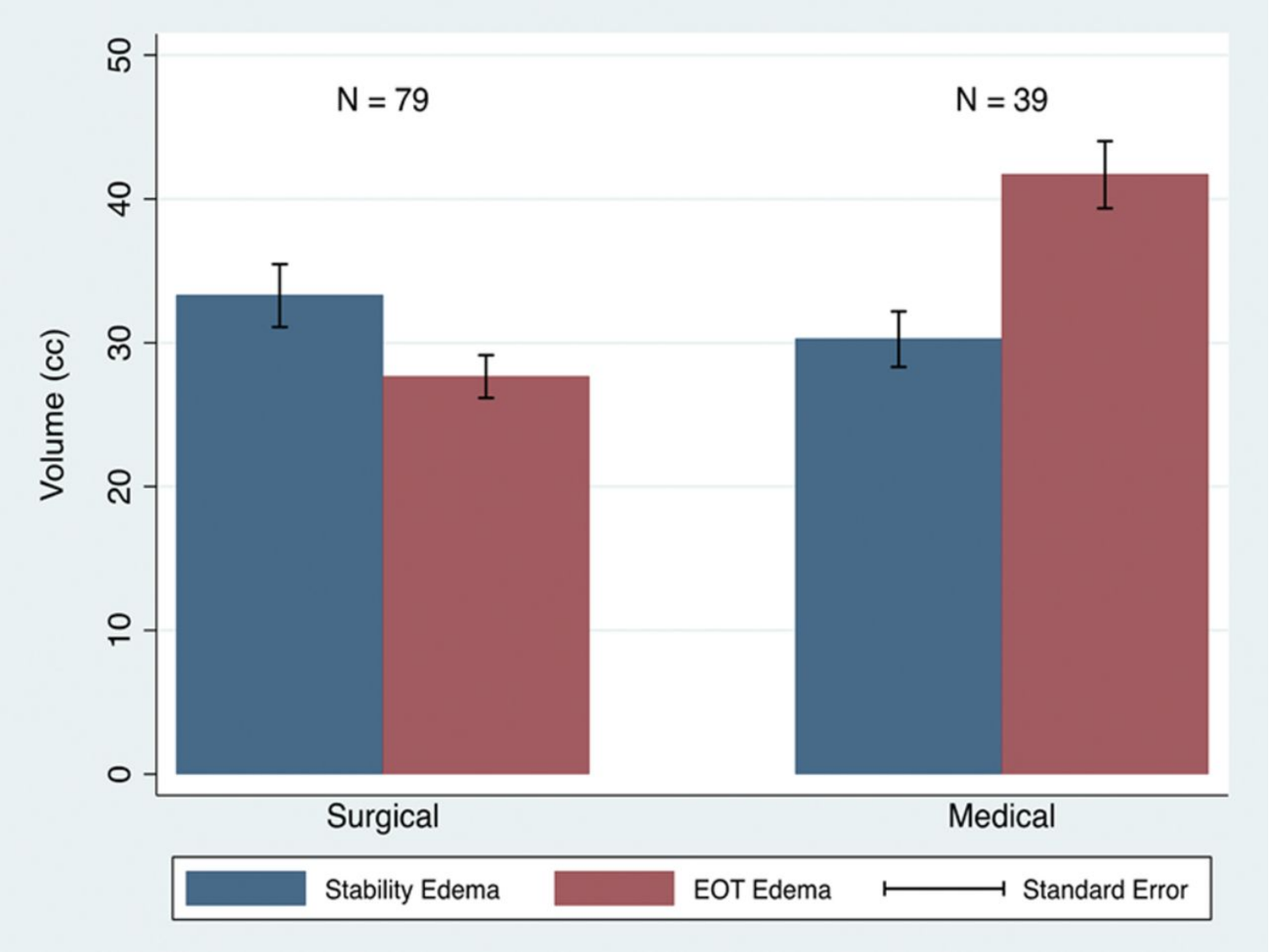
- Age 18-75
- GCS ≤ 13 or NIHSS ≥ 6
- Spontaneous supratentorial ICH ≥ 20cc
- Stable clot at second CT scan performed ≥ 6 hours after diagnosis

Exclusion

- Infratentorial ICH
- Vascular malformation or brain tumor
- Irreversibly impaired brainstem function

MISTIE II

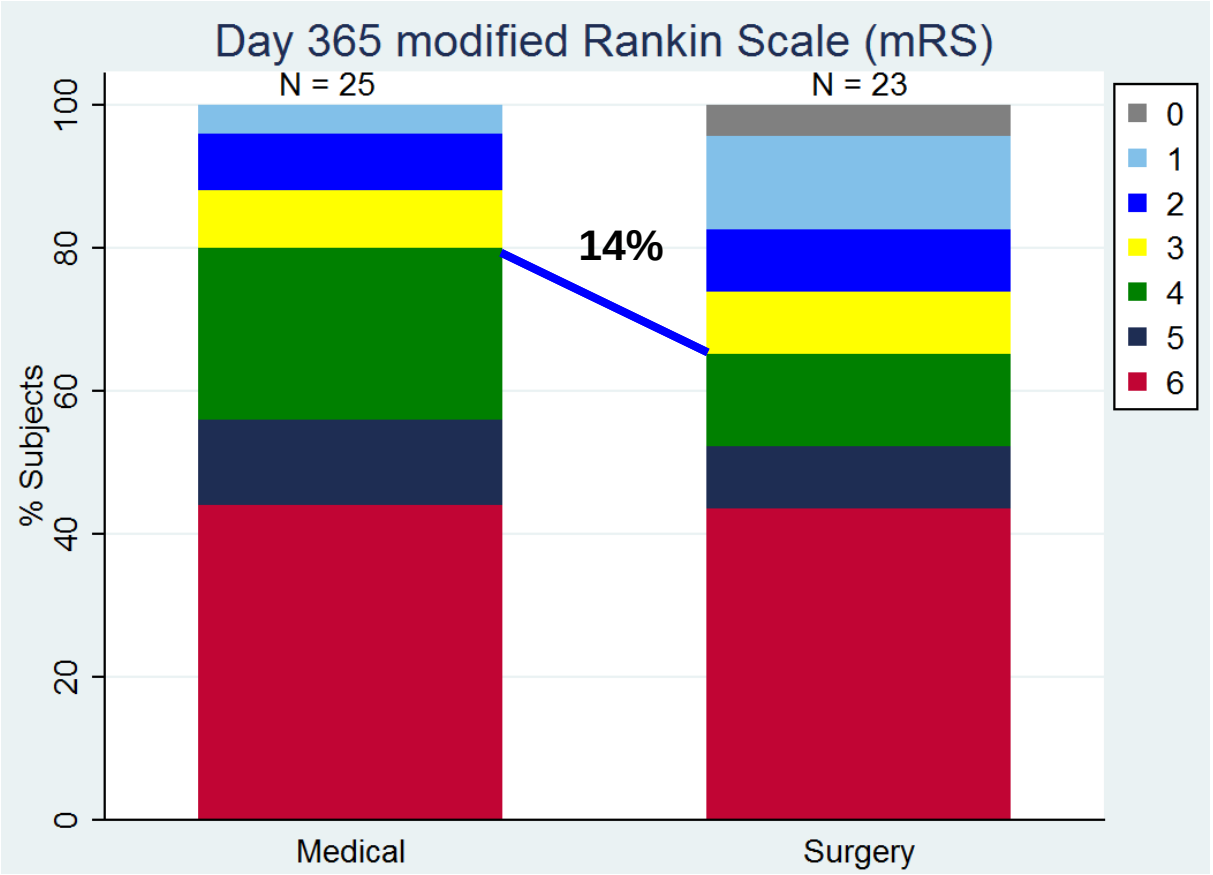
BLS and EOT edema volumes for the surgical (S+rt-PA and SO) and medical cohorts.



Mould W A et al. Stroke. 2013;44:627-634

MISTIE II

- Trend towards improved survival at 120 days with surgical tx, 47 vs 44%
- At 6 months, no change in mortality, but increased mRS 1, 2, and 3 in surgical tx, fewer mRS 4 and 5
- More separation of groups, increase in mRS 1, 2, 3 at 12 month follow-up
- Catheter placement along the long axis of the clot was an important factor in clot evacuation



MISTIE II – 365 days vs 180 days

- Greater benefit at 365 than 180 days
- 14% upward shift across mRS levels 5 to 0 at 365 days
- 14% fewer MIS-treated subjects in LTC facilities
- Shorter hospital stay for MIS-treated subjects
- Estimated acute-care cost savings of $44,000
- Procedure is simple, rapid and easy to generalize.

MISTIE II

"The greater the reduction in clot size
the better the patient outcome.
Volume reduction matters!"

Mechanism

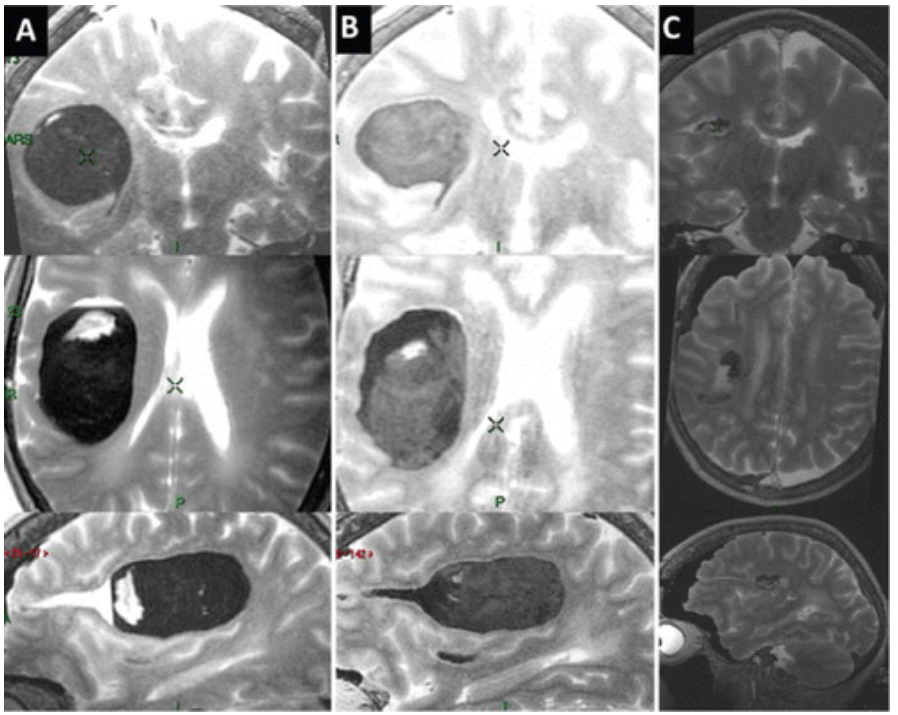
- Reduction of clot burden
- "Saving tissue at risk"
- 2° injury occurs over days

Benefits

- Most likely MIS increases independence
- Appears to improve function & decrease cost

Other Minimally Invasive Options

- Sonothrombolysis or MRgFUS (MR-guided focused ultrasound)
- Used for other neurosurgical indications
- With or without tPA
- Not in (live) humans… yet



Monteith, et al. J Neurosurgery. 2013

The Future…

- Early interventions likely to be most effective (inflammatory cascade, secondary injury, etc)
- Ongoing trials assessing benefits of:
  - Blood pressure targets
  - Hematoma removal using innovative surgical techniques with minimal associated brain injury or re-bleeding
  - Further assessment of medical therapies aimed at prevention of hematoma expansion
  - Assessment of therapies aimed at decreasing injury in peri-hematomal region

Questions/Discussion