# SPONTANEOUS INTRACEREBRAL HEMORRHAGE: MEDICAL MANAGEMENT

Neeraj Naval, MD

Baptist Neurological Institute

# Disclosures/ COI

Nothing to disclose (what happens in Vegas stays in Vegas)

No Conflict of interest

# Non-modifiable Impact Factors (ICH Score)

- Age: < 80 : 0
  > 80 : 1
- GCS score 13–15 : 0
  5–12 : 1
  3–4 : 2
- ICH location : Supratentorial : 0
  Infratentorial : 1
- ICH volume (AxBxC/2) < 30 mL : 0
  > 30 mL : 1
- IVH No : 0
  Yes : 1

Total: 0 - 6

# ICH Overview: (Outcome model)

| ICHS | Mortality (%) |
|---|---|
| 0 | 0 |
| 1 | 13 |
| 2 | 26 |
| **3** | **72** |
| 4 | 97 |
| 5 | 100 |

# Lecture Focus: Modifiable Impact Factors

Modifiable Risk factors for Outcomes aka Complications of ICH

- Mass effect (Hematoma expansion- Hemostasis)

  A) Blood pressure control

  B) Hemostatic therapy

  C) Reversal of bleeding diathesis

- Mass effect (Cerebral edema/ Intracranial HTN)
- Hydrocephalus (sec to IVH): CLEAR 3
- Seizures: ppx?
- Recurrent ICH

# Lecture Focus: EXCLUDED

- Reversal of NOAC (Dr. Rama/ Chen)
- Role of Surgery in ICH: STITCH, STICH 2 (Dr. Lopes)
- Role of Surgery in ICH: Incl. Minimally Invasive surgery (Dr. Lopes)

# ICH Overview: Impact

Approximately 500,000 new strokes occur every year in the United States, 15% of them are hemorrhagic strokes.

These numbers are expected to double during next 50 years.

- Increased longevity of the population.

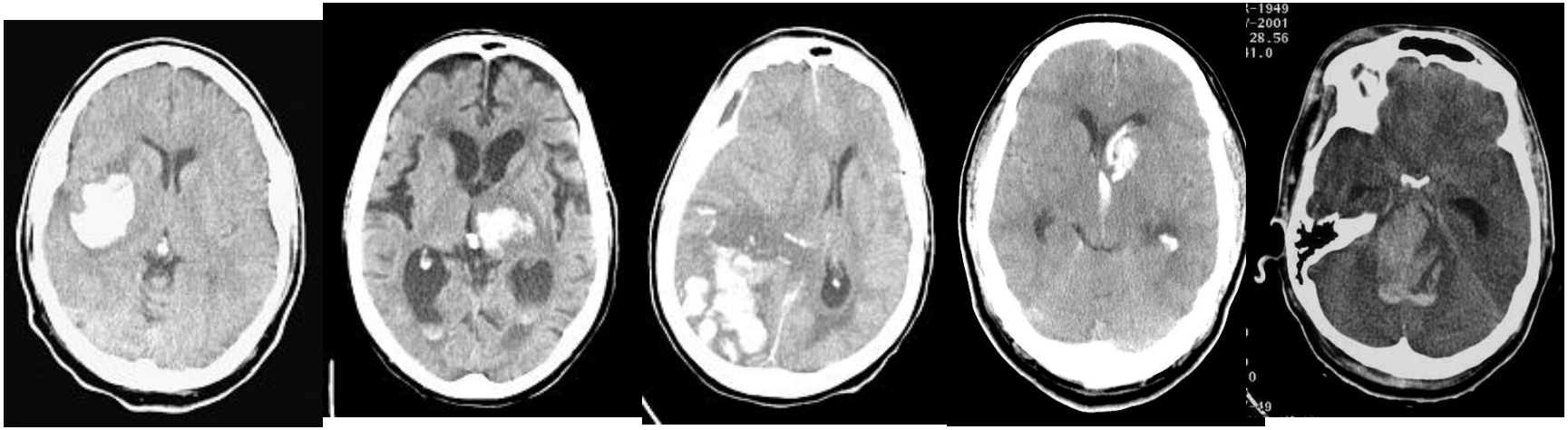
Overall population based mortality of ICH patients remains high:

- 6% die before reaching a hospital.
- 30 to 50% die within the first 30 days.
- GCS < 8 and ICH volume > 60 cc > 90% 30-day mortality

Independent living after ICH:

- After 1 month: 10%,
- After 6 months: 20%.

# ICH Overview: Location

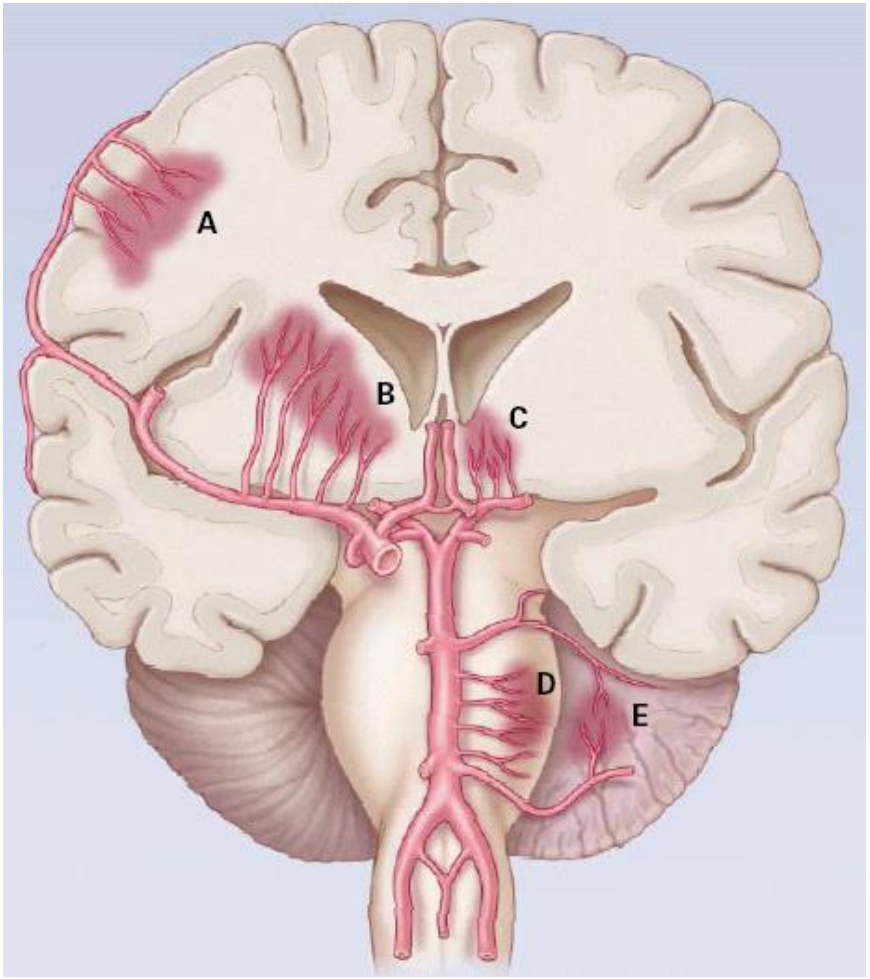


Putaminal Thalamic Lobar Caudate Pontine

# ICH: presentation

50% CAA
50% Other

Majority HTN




Qureshi; N Engl J Med 2001;344:1450-60

# ICH Overview: Etiology

PRIMARY ICH

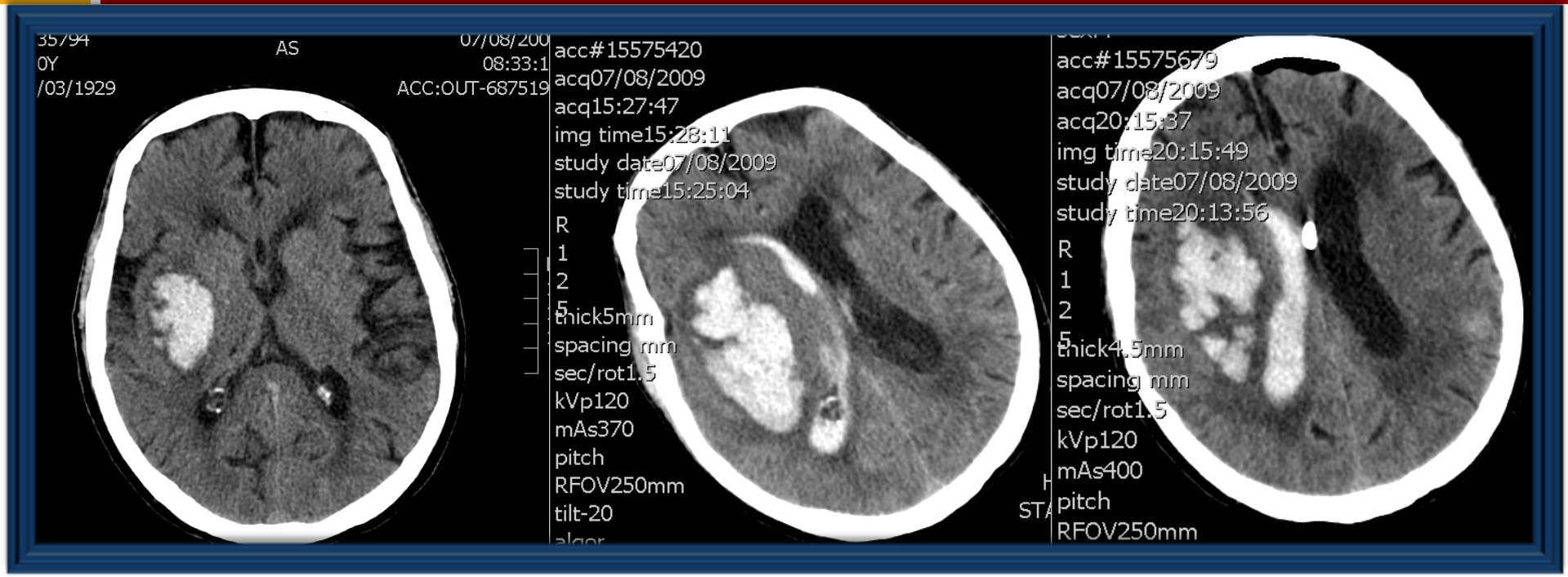
Hypertensive
Cerebral amyloid angiopathy
Cryptogenic

SECONDARY ICH

Trauma
AVM
Intracranial aneurysm
Coagulopathy
Hemorrhagic conversion of ischemic stroke
Dural sinus thrombosis
Intracranial tumor
Cavernous malformation
Dural AV fistula
Venous angioma
Cocaine use
CNS vasculitis/ RCVS

Mayer;Lancet Neurol 2005;4(10):662-72

# Mass Effect: Blood pressure/ Hematoma expansion



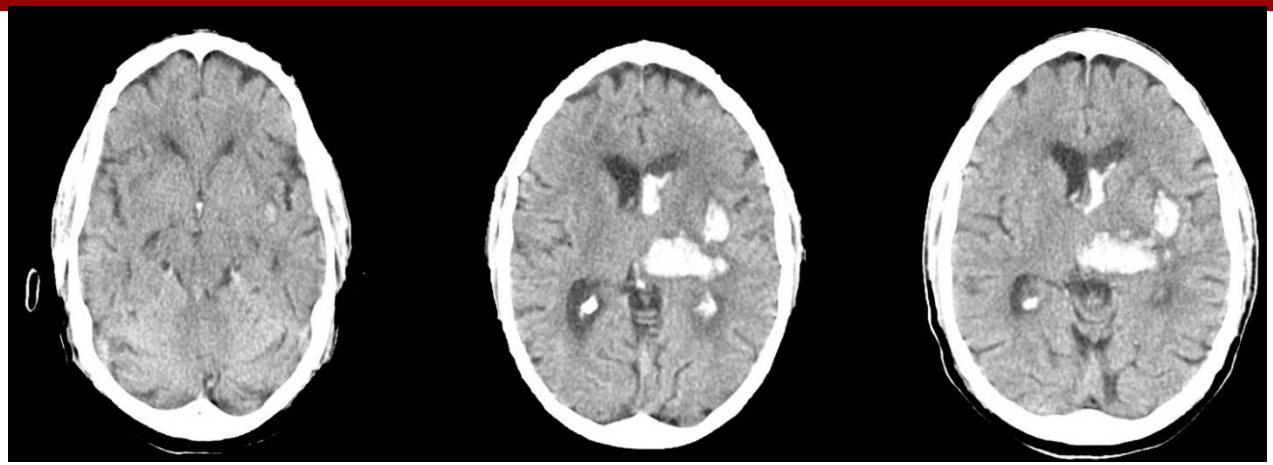

38%>33% growth over 24h

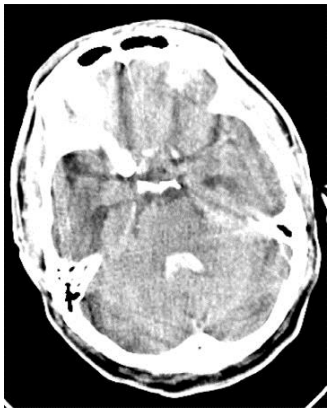
73% some growth over 24h

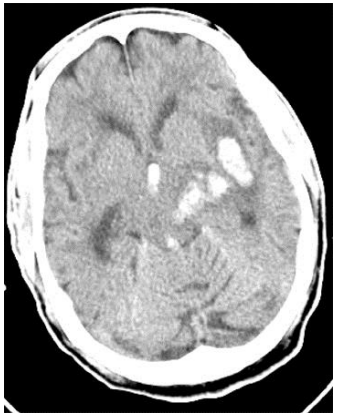
Independent predictor of bad outcome

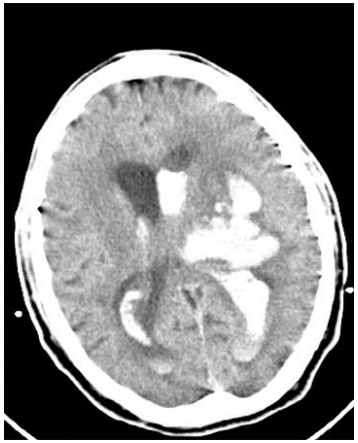
Davis; Neurology 2006;66(8):1175-81

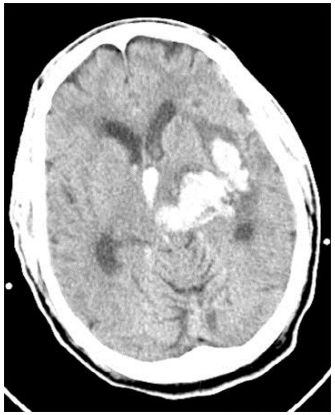
# Hematoma enlargement within 6 hours from symptom onset











# ICH and IVH: Complications

**Hematoma enlargement**

- Early hematoma growth in ~ 30% of ICH patients within 3 hours of onset can cause significant neurologic deterioration.

- 1 cc larger volume ICH = 7% more likely to have worse clinical outcomes

# Blood Pressure Targets – Association vs true evidence

Cause-effect

- Does increased Blood pressure cause more bleeding?
- Or is it a marker for more severe neurological injury (increased ICH volume = Kocher Cushing's reflex)

Treatment effect

- Does better blood pressure control actually lead to hemostasis?
- Or does it lead to worsening perihematomal ischemia?

# Best available evidence in 90s

1. Increased BP is associated with larger ICH volumes: SBP goal < 160 (Retrospectively observed association)

2. Small-moderate ICH volumes (<45 cc) are NOT associated with perihematomal ischemia (Powers et al)

ADC on MRI suggests inflammation (vasogenic edema) > ischemia (cytotoxic injury)

15-20% acute decrease in BP in first 6 hours not associated with decrease in critical perfusion.

MAP goal < 130 or SBP < 180 (1999 AHA guidelines)

# Available evidence in 21st century

- *ATACH pilot*: small Pilot study showing better hemostasis with SBP goal < 160 than historical controls.
- ATACH study showed *trends* towards decreased hematoma expansion and PHE in 110-140 compared to 140-170 compared to 170-200.
- ATACH 2 ongoing
- *INTERACT:* Mean 1.6 cc decreased in RCT with SBP goal < 140 compared to SBP < 180; 36% reduced risk of SHE, no difference in clinical outcomes (safe and non-inferior).
- AHA revised guidelines: If ICP elevation an issue, Control ICP with SBP goal < 180 until ICP controlled, otherwise SBP < 160. SBP < 140 is considered SAFE

# ?? Best available evidence in 21st century

## *INTERACT 2*

*Trend (p 0.06) towards improved functional outcomes with SBP < 140 compared to 180*

- *Significant difference if using ordinal analysis (not pre-specified)*
- *Median GCS 14, median ICH volume 11 cc*
- *75% of enrolled patients with ICH volume < 20 cc*
- *Restricted admission criteria to SBP < 220*
- *Nearly 70% patients enrolled in China*
- *No consistency in choice of HTN meds*
- *Investigators not blinded (higher rates of hemostatic therapy in study group)*
- *No difference in hematoma expansion rates (1.4 cc difference) or mortality (12% each)*

AHA revised guidelines x 2: SBP < 140 is SAFE and can be potentially effective in improving functional outcomes (Level of Evidence IIB) in patients similar to those enrolled in INTERACT 2.

# Mass Effect: Hemostasis: Novo7 trial

Phase 2 B trial for Activated factor 7

- 400 patients with 100 each in 40, 80, 160 mcg/kg and placebo within 4h symptom onset

| | Placebo | 40 | 80 | 160 |
|---|---|---|---|---|
| mRS 3-6 | 69% | 55% | 49% | 54% |
| Complications | 2% | ---------- | | 7% |

Mortality: 29% to 18%

# (Not So) FAST trial

**FAST** Placebo vs. rFVIIa (20µg/kg or 80µg/kg) within 4hr
*n*=841

Hematoma expansion

| 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 |
| 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 | — |

Functional outcome

No difference in good outcome, bad outcome or death

?benefit

ICH volume<60mL; Age≤70; ≤2.5h to treatment; IVH<5mL

Mayer;N Engl J Med 2008;15;358(20):2127-37+Stroke 2009;40:833-40

# Why did FAST fail?

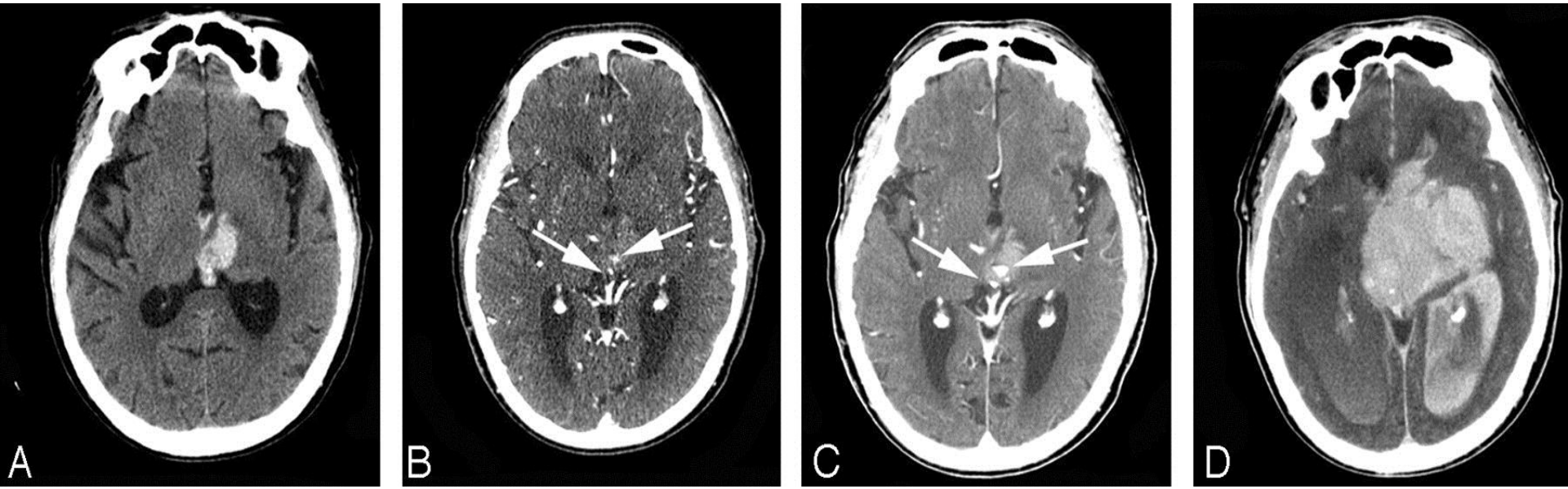
Mortality: Novo7: 26%, Placebo: 21%

- Randomization: IVH in 29% Placebo, 41% study drug
- Liberal inclusion criteria (age up to 80, GCS 6-8 OK, large ICH volumes ok)

- Post-hoc analysis: Benefit in Novo-7 group
- Age < 70
- ICH Volume < 60 cc
- IVH < 5cc
- Drug within 2.5h

- Too little, too late. Could we predict who would have expanded hematomas?

# SPOT SIGN



# Contrast extravasation/ Spot sign

- Spot sign +ve: 77% likelihood of hematoma expansion (Wada et al)

- Spot sign –ve: 4% likelihood of hematoma expansion (NPV 96%)

PREDICT TRIAL: > 33% increase or absolute increase of 6cc

PPV 60%

NPV 78%

Sensitivity: 51%

Specificity: 85%

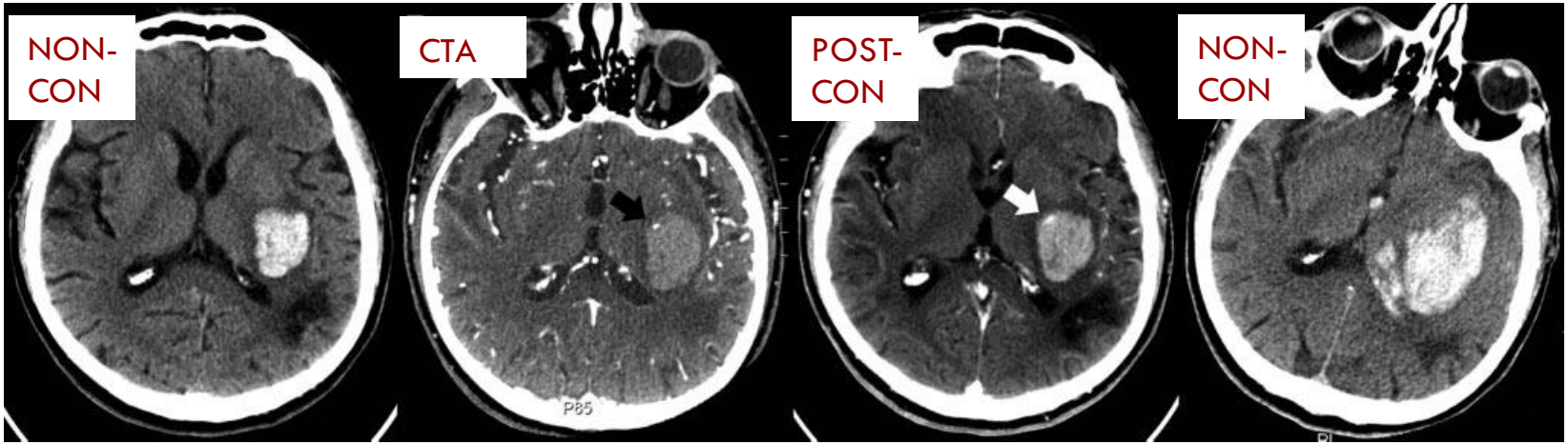
# SPOT SIGN

## CTA spot sign

| Spot Sign Characteristic* | Points |
|---|---|
| No. of spot signs | |
| 1–2 | 1 |
| ≥3 | 2 |
| Maximum axial dimension | |
| 1–4 mm | 0 |
| ≥5 mm | 1 |
| Maximum attenuation | |
| 120–179 HU | 0 |
| ≥180 HU | 1 |

| Accuracy Parameter | Hematoma Expansion* (95% CI) |
|---|---|
| Sensitivity | 88 (75–94) |
| Specificity | 93 (89–95) |
| Positive predictive value | 69 (57–79) |
| Negative predictive value | 98 (95–99) |
| Positive likelihood ratio | 12.4 (8.2–18.7) |
| Negative likelihood ratio | 0.13 (0.07–0.27) |
| Accuracy | 92 |

*Hematoma expansion defined as >30% or >6 mL increase from the initial ICH volume.




Delgado; Stroke 2009; Jun; EPUB ahead of print; Wada; Stroke 2007;38:1257-1262

# Contrast extravasation/ Spot sign

What can we do about this data?

- Hemostatic agents…… ongoing trials (STOP-IT, SPOTLIGHT study)
- More aggressive BP control…….. SBP goal 140?
- Reversal of platelet dysfunction…… PLT transfusion (PATCH trial)?
- Reversal of coagulopathy…….high risk patients?
- TRIAGE

# Coagulopathies in a snapshot

- Warfarin: PCC >> FFP (Sarode et al), + Vit K IV
- NOAC: PCC (Xa), specific inhibition (DTI)
- tPa: NS: Cryoprecipitate + platelets +/- FFP

  S: Antifibrinolytic therapy (tranexamic acid/ Amicar)
- Heparin gtt: Protamine (no more than 50mg; administration time based)
- LMWH (lovenox): 0-8h: 1 mg protamine: 1 mg lovenox

  8-12h: 0.5mg Protamine: 1 mg lovenox

  12-24h: None unless surgery/ ongoing bleeding or ARF/ CRF
- Fondaparinaux: ??

# ASA/ Plavix Reversal

- ASA: ? Platelets……PATCH trial
- Plavix: Half life 8 hours…… ?PLT/ ddAVP (MOA- vWF)
- DDAVP: Uremic platelet dysfunction, ? Anti-PLT (PFA correction)

<u>Indication for PLT transfusion</u>

A) Hematoma expansion/ Neurological deterioration
B) Spot Sign +
C) Surgical intervention (including EVD)
D) Abnormal PFA

# Intracranial HTN: Clinical signs

NEUROLOGICAL

Blown pupils, anisocoria (new)

Altered mental status

Decerebrate/ decorticate posturing

Increase in ICP (if monitored)

NON-NEUROLOGICAL

Cushings response: Hypertension, reflex bradycardia, irregular respirations)

Nausea, vomiting

# ABCs

Airway: GCS < 8

GCS > 8 with impending neurological deterioration

Cough/ gag/ increased secretions (Coplin et al)

Breathing: Ataxic/ cluster breathing patterns

Sat probe: Avoid hypoxia, sat goals > 94%

ABG/ ETCO2: Co2 goal 28-32

Circulation: MAP > 70

CPP > 60 (TBI)/ > 70 (comatose ICH/SAH), ICP < 20

# Hyperventilation

Decrease in $PCO_2$ from 40 to 30 mmHg --- Cerebral vasoconstriction --- 3% decrease in CBF/ 1 mmHg decrease in $PCO_2$ (30% reduction in CBF) --- decreased ICP

Prolonged Cerebral vasoconstriction --- Cerebral Ischemia

CSF Ph normalizes --- Rebound Hyperemia --- Reperfusion Injury --- Rebound Increase in ICP

Caution: Avoid prophylactic use, avoid prolonged use

# Hyperosmolar therapy

## Options

Mannitol (1-1.5 gm/kg)

Hypertonic saline (3% bolus / 23.4% 30 cc ‘bullet’)

# Mannitol

1-1.5 gm/kg 20% mannitol, acts within minutes, peaks at 1 h duration 4-6 hours.

Failure to respond: 2nd dose 1.5-2gm/kg

Can give through peripheral IV

Watch for Hypotension secondary to increased diuresis

# Hypertonic saline

23.4% Saline 30 cc bolus, may repeat with second 'bullet'

Requires Central venous access

Follow with maintenance 3% saline infusion with Na goal 145-155

Effective in 'mannitol failures'

Watch for acute hypotension

# Mannitol vs Hypertonic saline

**Table 1.** Study characteristics

| Study Characteristics | Study | | | | |
|---|---|---|---|---|---|
| | Afifi et al (27) | Battison et al (14) | Francony et al (18) | Ichai et al (17) | Schwarz et al (13) |
| Study year | 2003 | 2005 | 2008 | 2009 | 1998 |
| Country | Egypt | UK | France | France | Germany |
| Subjects (n) | 40 | 9 | 20 | 34 | 9 |
| Age (yr) | 36 (6) | Not available | 40 (14) | 36 (15) | 57 (11) |
| Cases | Tumor (n = 40) | TBI (n = 6)<br>Subarachnoid hemorrhage (n = 3) | TBI (n = 17)<br>Intracranial hemorrhage (n = 2)<br>Stroke (n = 1) | TBI (n = 34) | Stroke (n = 8)<br>Intracranial hemorrhage (n = 1) |
| Mannitol formulation | 20% | 20% | 20% | 20% | 20% |
| Sodium formulation | 3.0% sodium chloride | 7.5% sodium chloride + 6% dextran-70 | 7.45% sodium chloride | Sodium lactate | 7.5% sodium chloride + hydroxyethyl starch (60 g/L) |
| Mannitol dose | 5.49 mosm/kg | 249 mosm | 255 mosm | 1.74 mosm/kg | 220 mosm |
| Sodium dose | 5.49 mosm/kg | 250 mosm | 255 mosm | 1.65 mosm/kg | 257 mosm |
| Baseline ICP (mm Hg) | | | | | |
| Mannitol | 31 (4) | 24.0 (18.8, 25.9)[a] | 31 (6) | N/A | 26.1 (1.5) |
| Sodium | 31 (4) | 22.0 (20.1–26.3)[a] | 27 (3) | N/A | 28.6 (4.8) |
| Definition of ICP control | <20 mm Hg | <18 mm Hg | >20% below baseline | Decrease >5 mm Hg or absolute <20 mm Hg | >10% below baseline |
| ICP control | | | | | |
| Mannitol | 16 of 20 (80%) | 14 of 18 (78%) | 10 of 10 (100%) | 19 of 27 (70%) | 10 of 14 (71%) |
| Sodium | 19 of 20 (95%) | 16 of 18 (89%) | 9 of 10 (90%) | 28 of 31 (90%) | 16 of 16 (100%) |
| ICP decrease | | | | | |
| Mannitol | 13 (5) | 7.5 (5.8–11.8)[a] | 14 (8) | 5 (2) | 4.6 (4.7) |
| Sodium | 12 (5) | 13.0 (11.5–17.3)[a] | 10 (5) | 8 (2) | 11.0 (7.1) |

ICP, intracranial pressure; TBI, traumatic brain injury.

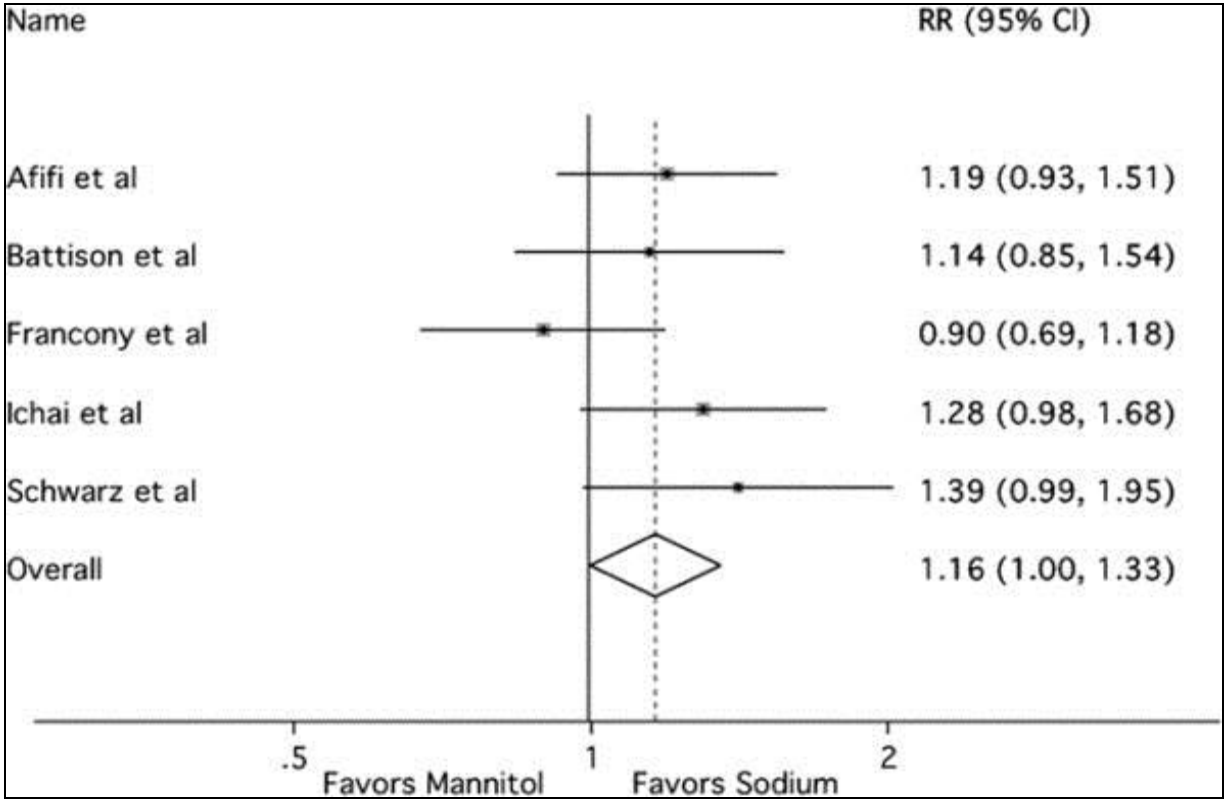
Continuous measures are expressed as mean (sd), except ICP measurements from Battison et al,[a] which are expressed as median (interquartile range). ICP control denotes the proportion of episodes of elevated ICP successfully treated with a randomized dose of study medication. ICP decrease denotes the maximum decrease in mean ICP (mm Hg) within 60 mins of study drug administration.

**Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: A meta-analysis of randomized clinical trials *.**

Kamel, Hooman; Navi, Babak; Nakagawa, Kazuma; Hemphill, J; Claude III MD, MAS; Ko, Nerissa

Critical Care Medicine. 39(3):554-559, March 2011.
DOI: 10.1097/CCM.0b013e318206b9be

# Relative risk of successful control of elevated ICP

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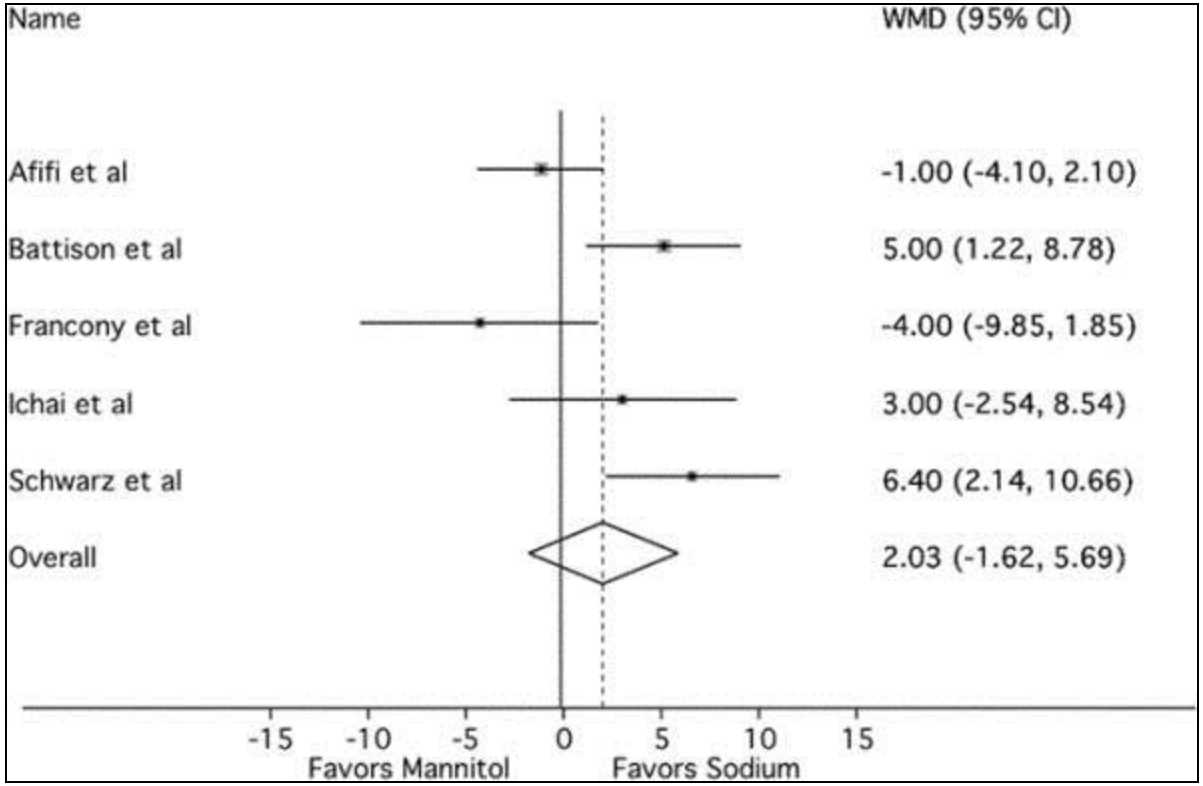
# Difference in mean quantitative reduction of ICP

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# Advantages

## Mannitol

May be given through PIV

## 23.4% saline

Higher reflection coefficient

Maintains intravascular volume status

May be followed by 3% saline as continuous infusion

?More robust action

?Longer duration of action

? Greater impact on brain oxygenation (Oddo et al)

# ICP monitor / IVC placement

Intraventricular catheter (IVC) facilitates CSF drainage

ICP monitoring useful with unreliable clinical exam (GCS < 8)

Cerebral herniation *possible* without ICP elevation

Over-drainage especially in setting of cerebellar lesions can cause upward herniation

# Brain Code Supportive treatment

HOB > 30 degrees

Minimize neck compression

Sedation, minimize agitation

Maintain Volume status

Maintain Circulatory status (MAP goals)

*Seizure prophylaxis*

*Glycemic control*

*Goal of normothermia*

# Seizures

Incidence of seizures with ICH: Lobar 14% seizures, deep 4% (Bladin et al)

Phenytoin associated with worse outcomes in ICH, CVA, SAH, TBI.

Naidech et al: 10-fold increase in poor outcomes with phenytoin

*Fatal Flaws*

*ICH volume, IVH volume and location were NOT a predictor of outcomes*

*Difference in ICH volume in 2 groups > 20 cc, admission GCS 10 to 14*

# Seizure Prophylaxis: Counter-argument

Up to 26% of ICH patients could have only somnolence as manifestation of NCSE if monitored using cEEG monitoring (*Vespa et al*): 26%

Break up by location: 28% lobar, 21% deep.

Recommendation:

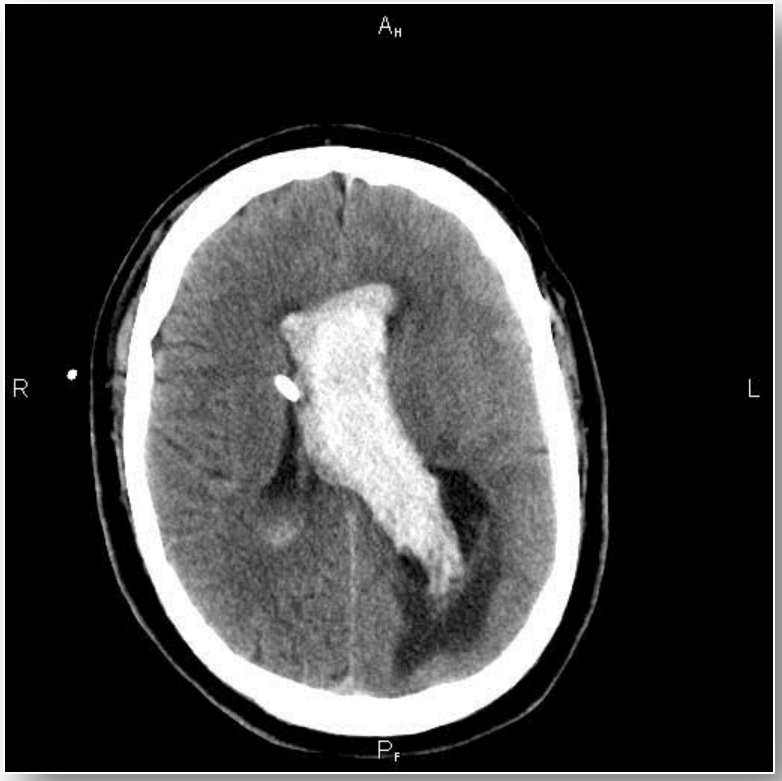
Routine prophylaxis for spontaneous ICH is NOT recommended.

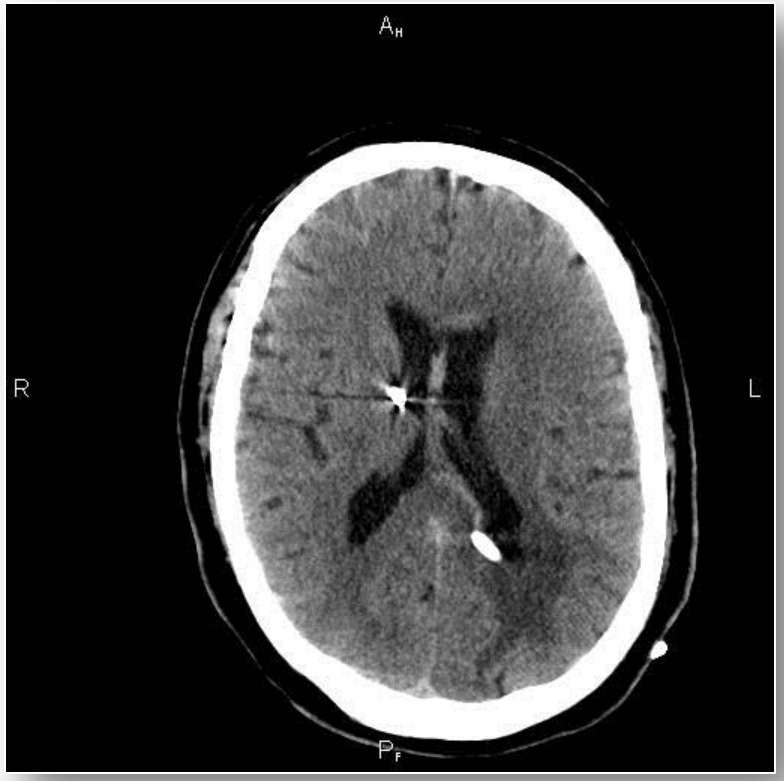
Recommendation is relevant for SPONTANEOUS ICH.

If considering AED for any reason (temporal ICH, underlying structural lesion, craniotomy, cocaine use), consider alternative to PHT for *prophylaxis* for lobar ICH

cEEG monitoring is highly advisable in patents with AMS following ICH.

# Hydrocephalus/ IVH: Tuhrim et al



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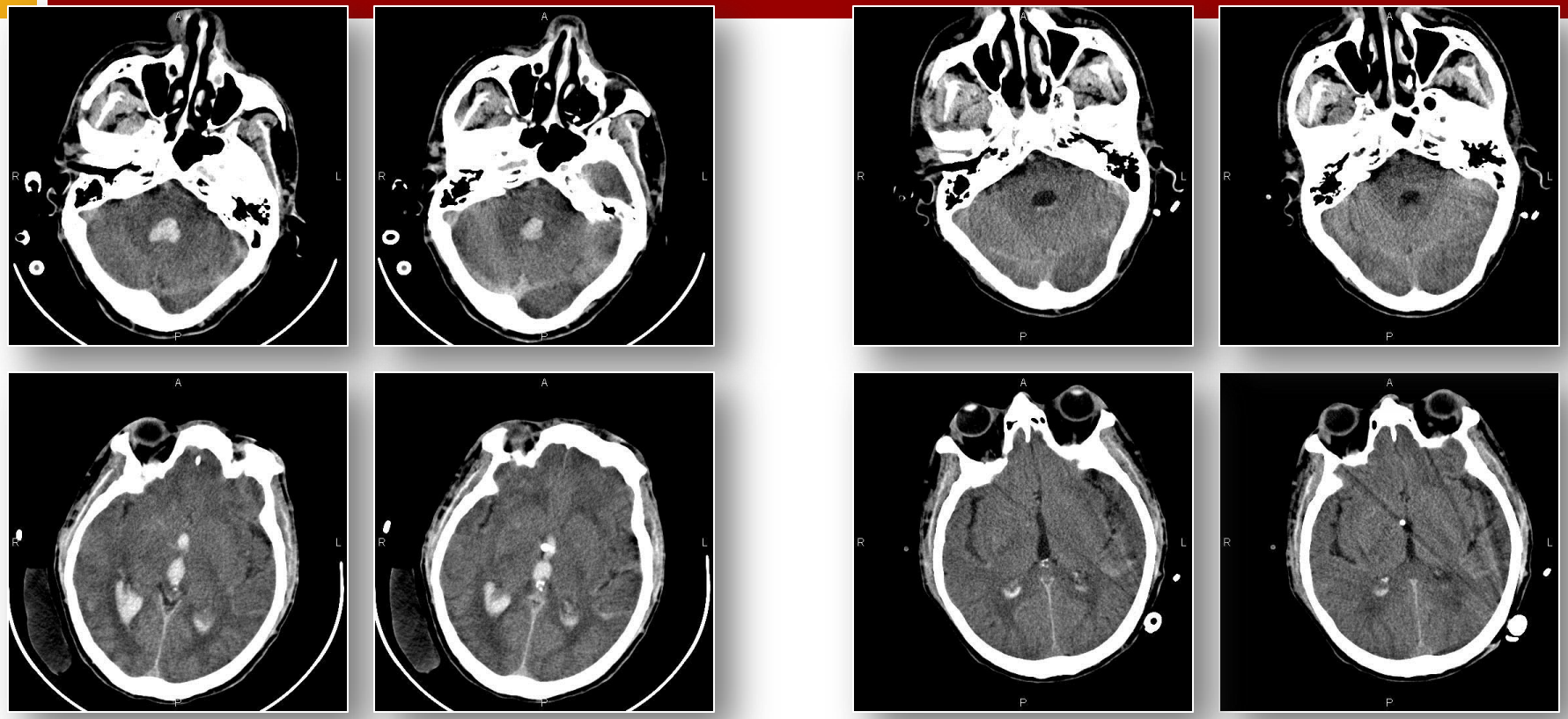
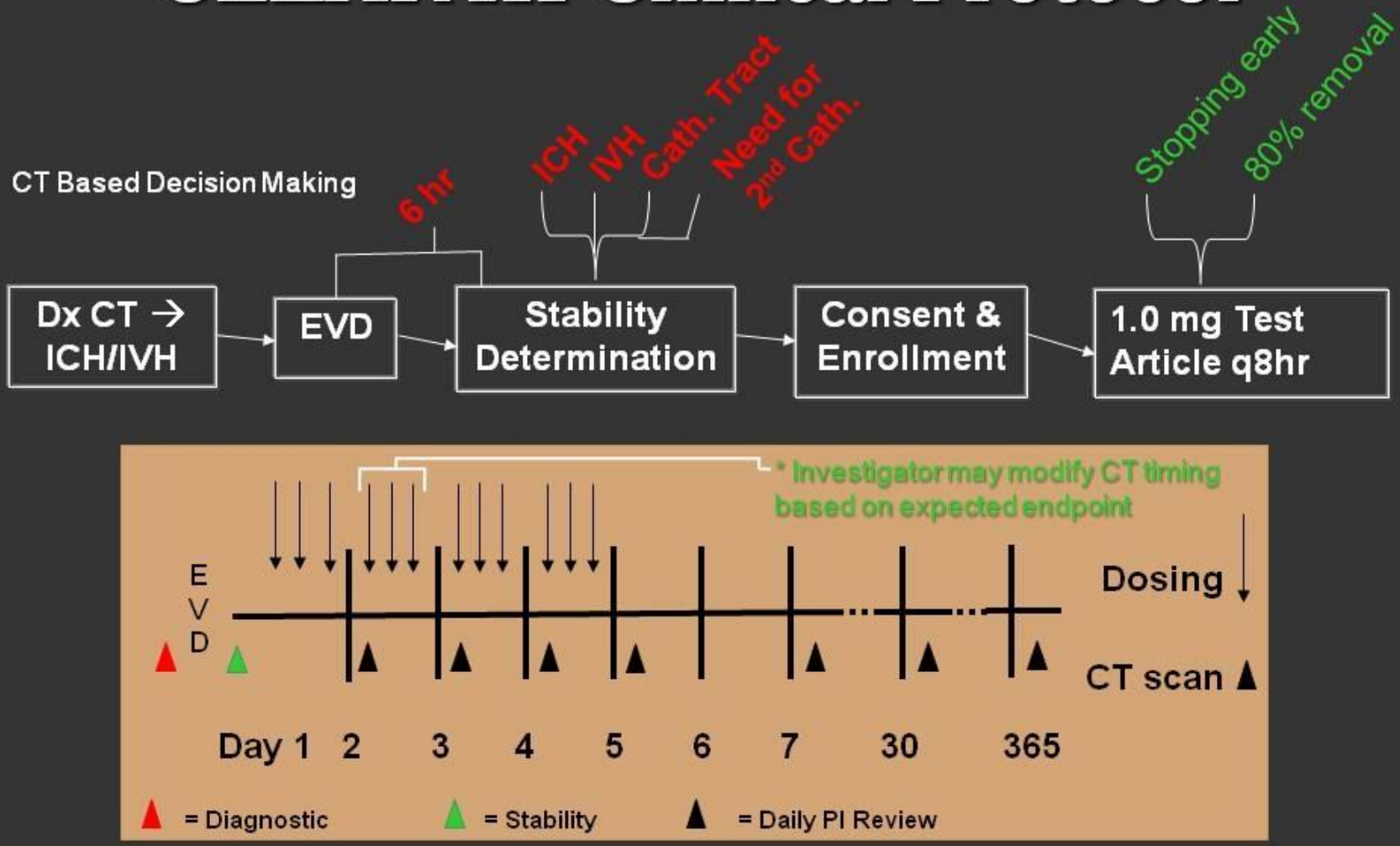
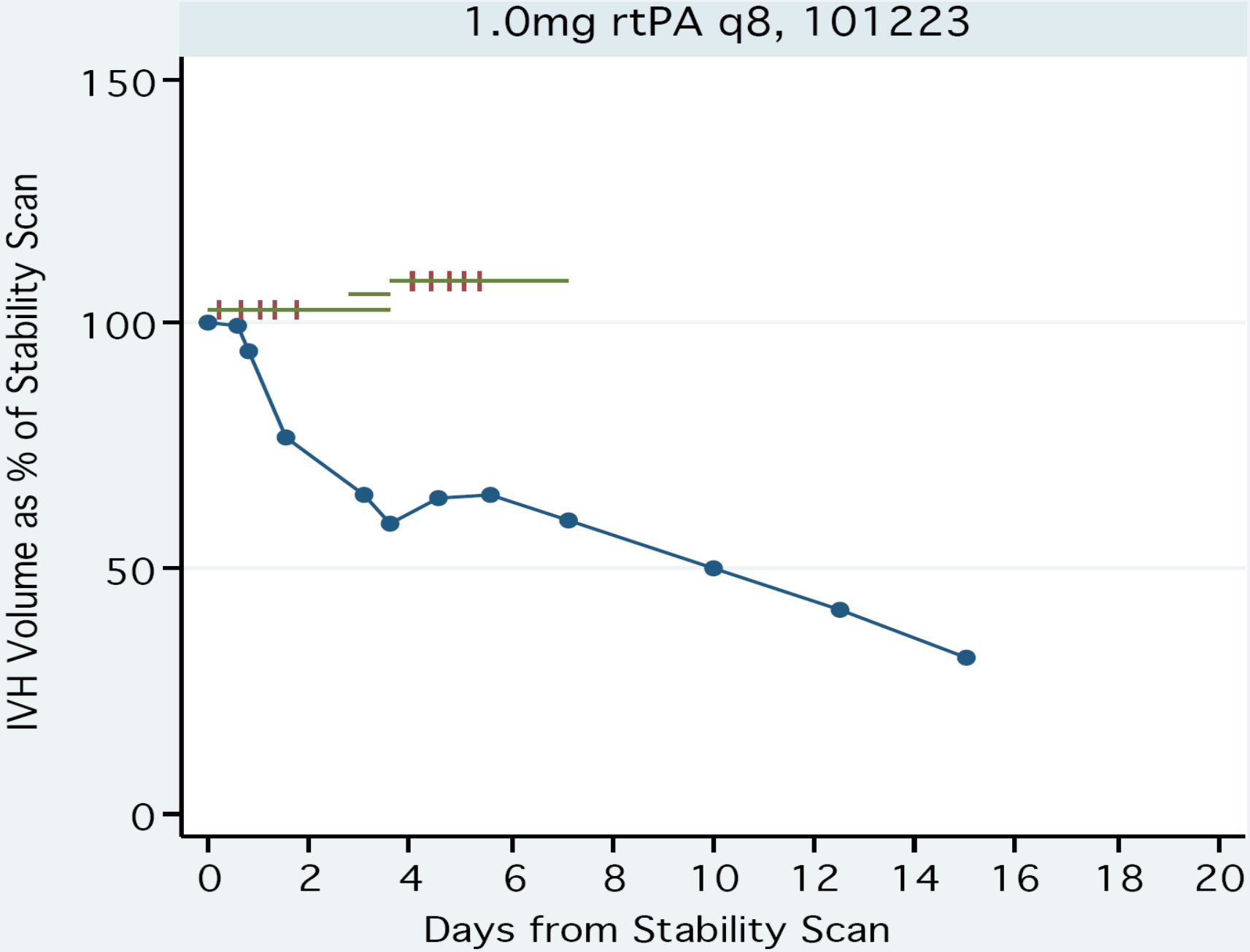
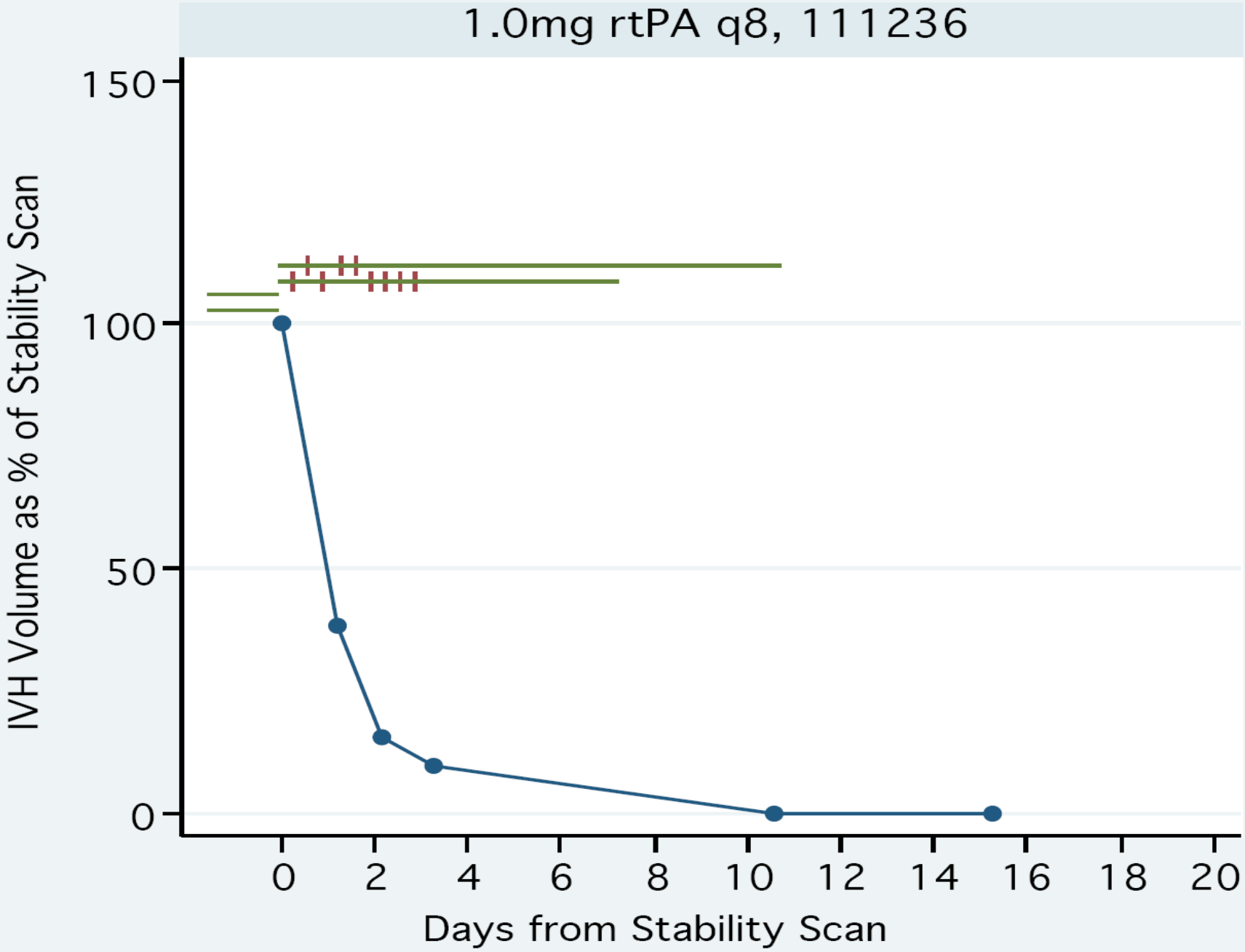


# CLEAR III Clinical Protocol




1.0mg rtPA q8, 101223
IVH Volume as % of Stability Scan
150
100
50
0
0
2
4
6
8
10
12
14
16
18
20
Days from Stability Scan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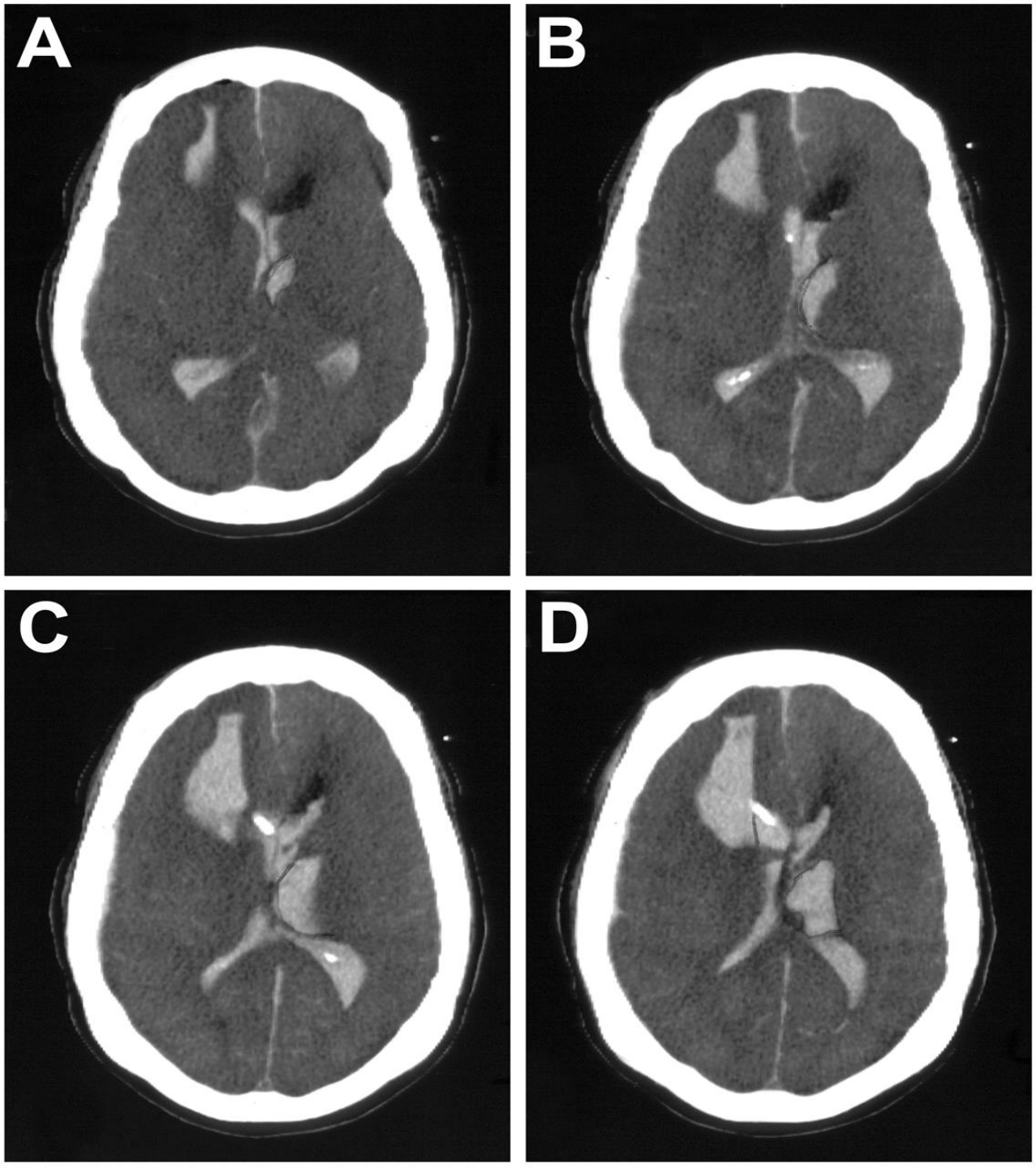
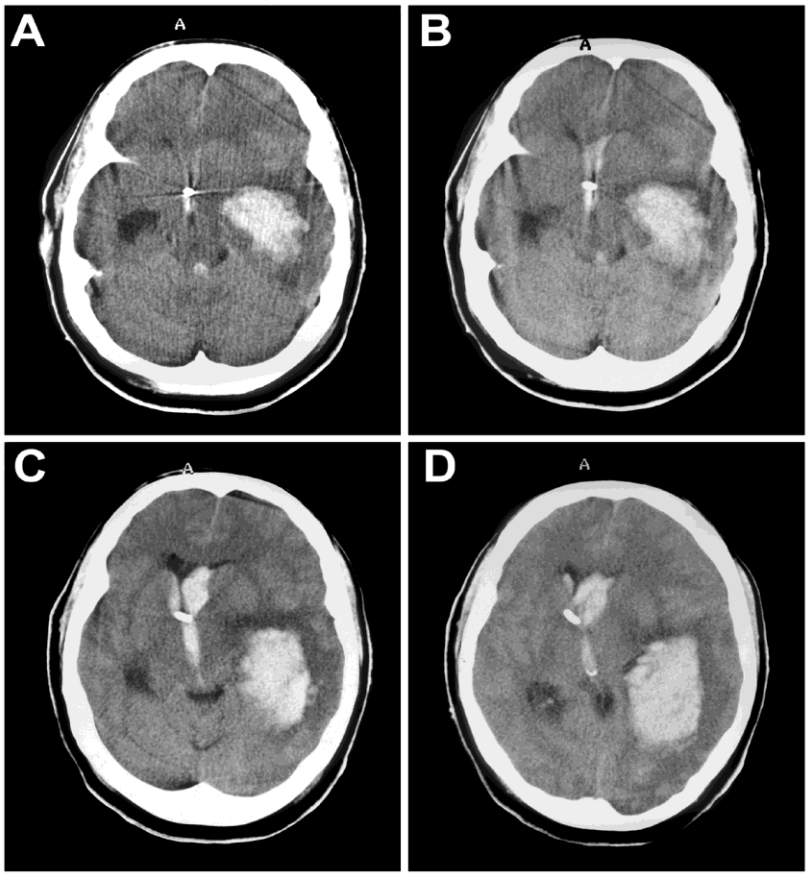


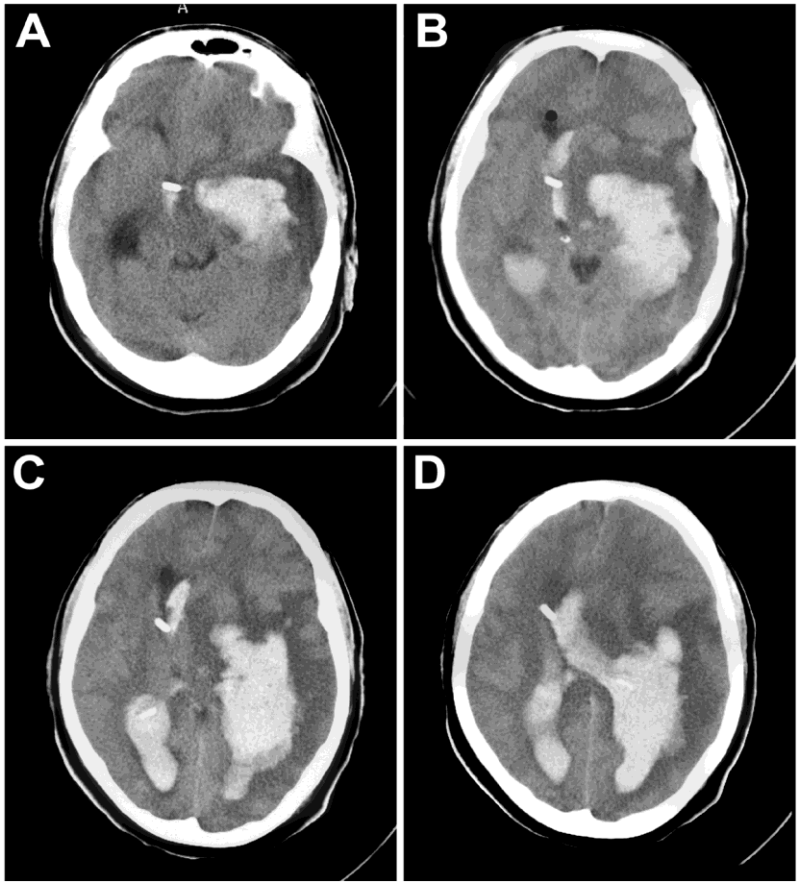

**Subject**

**Post-rebleed**

# IVH expansion




before




after

# CLEAR 3 Results

Pragmatic Phase 3 randomized control trial for tPa vs saline through EVD

Outcome assessment at 6 months:

Primary endpoint: mRS 0-3: 48% tPa vs 45% control (NS)

Secondary outcomes:

eGOS: ND

Mortality lower in tPa group: p 0.006, NNT 10

66% home/ rehab (tPa) vs 56% (control): p 0.06

Bleed: 2.6% vs 2% (safe)

Infection rates marginally lower (???)

# CLEAR 3 Results

Subgroup analysis:

Clot lysis more effective in post hoc analysis in……..

A) IVH volume over 20 cc (10% higher rates of mRS 0- 3)

B) Time to treat < 48h

So what now……. CLEAR 4? 5? 6?

# ICH: MISTIE

## Stereotactic thrombolysis/aspiration

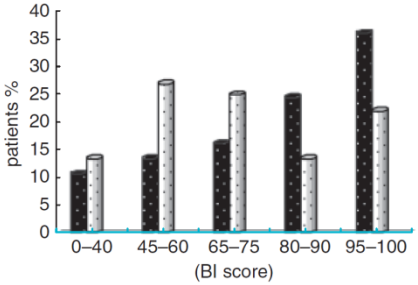
**MINIMALLY INVASIVE CRANIOPUNCTURE**

RCT minimally invasive surgery for basal ganglia ICH

Cannula placed inside clot and 10,000U-50,000U urokinase injected followed by aspiration (dose based on hematoma volume)

*n*=465

**90d outcome**




| | +tx | -tx |
|---|---|---|
| **MRS 0-2** | **63%** | **41%** |
| **Dead** | **8%** | **9%** |

MISTIE

RCT minimally invasive surgery for basal ganglia ICH

Cannula placed inside clot and tpa 1mg q8h x max 72h injected and aspirated until:
1. ICH volume 10cc
2. 80% decrease
3. Dose limit reached

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# Recurrent ICH: Vascular imaging

- Cerebral angiography

  - To make the etiological diagnosis in cases of:
    - Aneurysms
    - AVM's
    - Vasculitis
    - Dural AV fistula

# Vascular imaging

- Cerebral angiography
  - In young patients (< 45 y/o) w/o risk factors for ICH, the yield of angiography can reach 48% in putaminal, thalamic and posterior fossa ICH.
  - In young patients with lobar ICH, yield of angiography can reach 65%.
  - The yield of cerebral angiography in primary IVH is high regardless the age of the patient (50 to 67%), commonest cause AVM > aneurysm.
  - In this study of 206 ICH patients, any patient > 45 y/o with h/o hypertension, and hypertensive on presentation with ICH in "classic" locations (BG/ thalamus), the yield of angiography was ZERO *(Zhu et al)*

# Recuurent ICH: CTA/ MRI

- MRI
  - To make the etiological diagnosis in cases of:
    - Brain tumors (Primary)
    - Brain mets: (Lung, Breast, Renal, Melanoma, Choriocarcinoma, Thyroid)
    - Cavernous malformations
    - Amyloid angiopathy
    - Venous infarctions (CTV)
- CTA
  - To make the etiological diagnosis in cases of:
    - Aneurysms
    - AVMs
    - (Spot Sign)

# ICH Recurrence risk

- Anticoagulation: Hold for 7-10 days (shorter in patients with prosthetic valve)
- Reversal based on severity of bleed and indication for AC
- Assess risk-benefit of long term AC in A Fib (CHADS 2 score/ HAS-BLED).
- Assess alternatives to AC (IVC filter, anti-PLT)
- Assess risk for recurrent bleed (high with cortical/ amyloid ICH, low with Hypertensive bleed)

# ICH: Recurrence risk

- Anti-platelets: Hold for 7 days; assess risk vs benefit of long term anti-platelet therapy.

- Statins: controversial (SPARCL vs met-analysis)
  - If lobar ICH and 'weaker' indication for statins (hypercholesterolemia) or strong indication (CAD/ CVA) but low LDL, may be advisable to stop statins
  - If deep ICH (hypertensive) and strong indication for statins (h/o MI, CVA), may continue
  - Acutely may lower peri-hematomal edema

Thank you for allowing me to speak beyond my allotted time