Tranexamic Acid for Protection in Subarachnoid Hemorrhage (The TAP-SAH Trial)

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NETT Retreat

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Disclosures

- No relevant disclosures

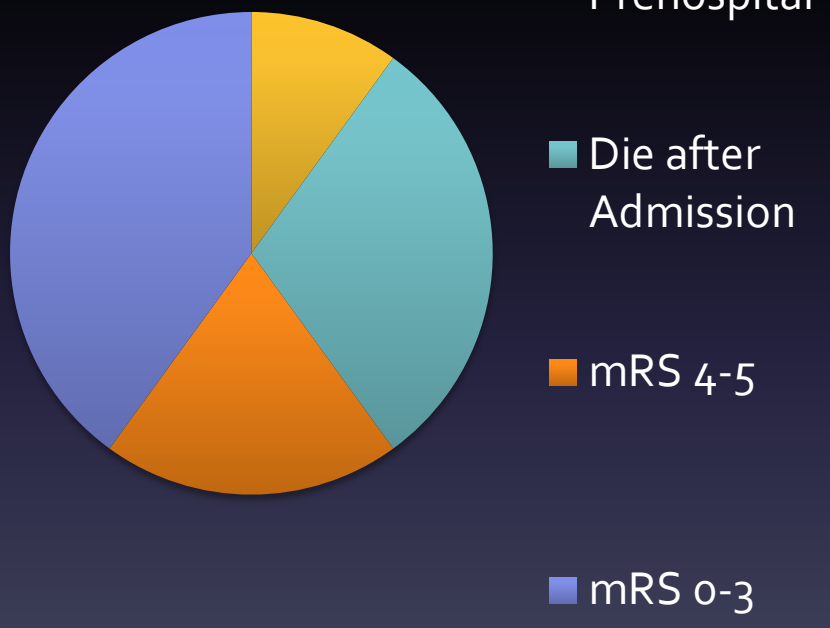
Impact of aSAH

- ~30,000/ year in the US
- Mortality as high as 45%
- Significant morbidity among survivors

Connolly, Stroke 2012

Outcomes following aSAH

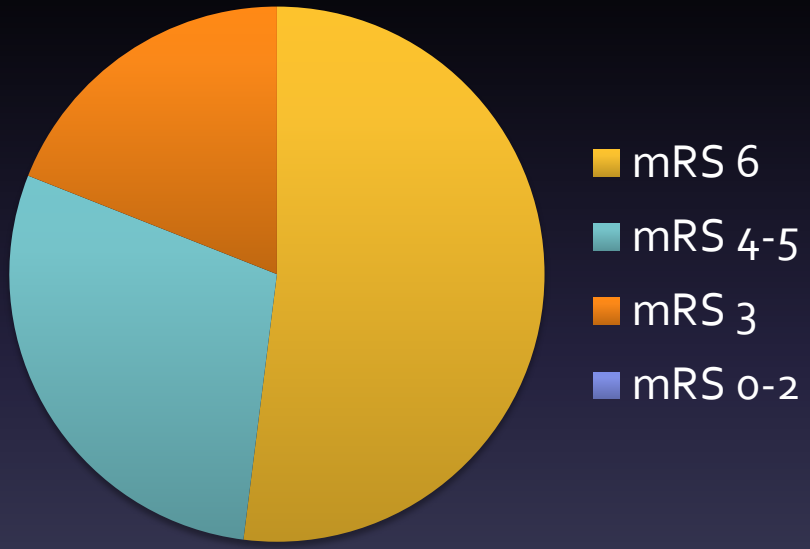
- 10% die pre-hospital
- 30% die after admission
- 20% mRS 4-5 at 6 months
- 40% mRS 0-3 at 6 months



Rinkel, Lancet Neurology 2011; Lovelock, Neurology 2010; Niuewkamp, Lancet Neurology 2009.

Outcomes if Rebleeding

8-23% rebleed after arrival, half of those in first six hours



- 52% die
- 29% mRS 4-5 at 6 months
- 19% mRS 3 at 6 months
- 0% mRS 0-2 at 6 months

Ohkuma, Stroke 2001; Naidech, Arch Neurology 2005; Kassell, Neurosurgery 1983

Unadjusted Poor Outcomes Attributable to Rebleeding

- 40-60%

Current Data

No proven interventions to prevent rebleeding

Table 3 Antifibrinolytic therapy after aneurysmal SAH

Reference	Study design	Antifibrinolytic	Incidence rebleeding, antifibrinolytic vs control
Hillman et al. [3]	Randomized, prospective, multicenter study of patients with SAH verified within 48 h of first hospital admission $N = 254$ TXA $N = 251$ controls	TXA at diagnosis and every 6 h until aneurysm occlusion or 72 h	2.4 vs. 10.8% ($P < 0.01$)
Harrigan et al. [6]	Retrospective review $N = 356$	Short-term EACA administered before aneurysm surgery, which occurred an average of 47 h after admission	1.4%
Starke et al. [16]	Prospective, observational study $N = 73$ treated with EACA $N = 175$ controls	Short-term EACA before aneurysm treatment	2.7 vs. 11.4% ($P = 0.019$)

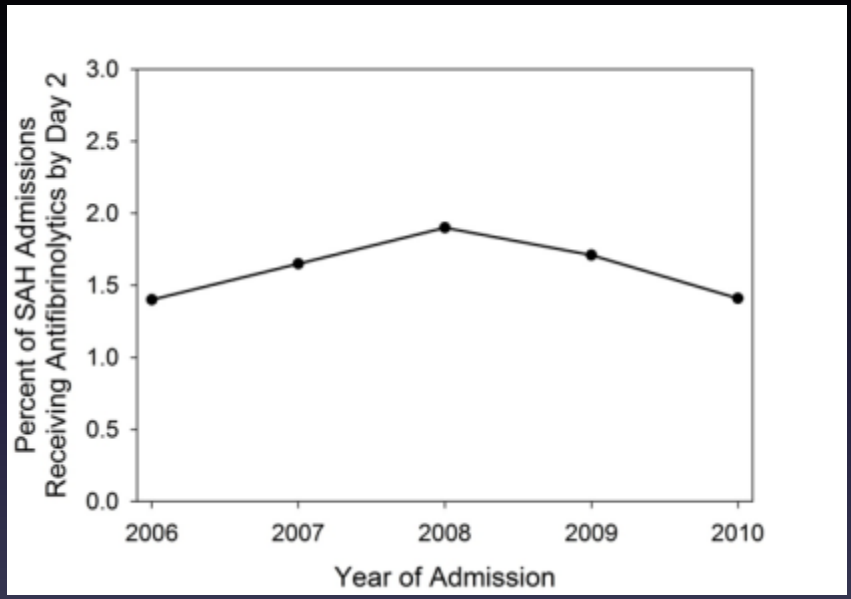
Hillman, J Neurosurg 2002; Harrigan, Neurosurgery 2010; Starke, Stroke 2008

AHA/ASA Recommendations

- *"For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindications, short term (<72 hours) therapy with tranexamic acid or aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding (Class IIa; Level of Evidence B). "*

Current US Practice – Clinical Equipoise

- From 2006-2010, only 1.6% of SAH patients received antifibrinolytics
- Midwest and Northeast regions were more likely to give antifibrinolytics



Adeoye, Neurocritical Care Conf 2011

Proposal

- Phase 3 double-blind randomized placebo controlled trial
- Intervention – Tranexamic acid 1gm IV within 12 hours of symptom onset then every six hours for 72 hours or until aneurysm is secured
- Primary Outcome – proportion of good outcome at 6 months using sliding dichotomy for the mRS
- Secondary Outcomes – GOSE at 6 months, Mortality at hospital discharge and 6 months, rebleeding rates, thromboembolic complications

Inclusion Criteria

- CT with acute SAH suspicious for aneurysm rupture
- 18 – 80 years of age
- GCS >/= 6 at time of randomization
- Study drug administered within 3 hours of enrolling hospital arrival

Exclusion Criteria

- Pregnancy
- GCS 3-5
- Fixed dilation of either or both pupils
- Cardiac arrest at any point between ictus and randomization
- ?Deterioration of >/=4 points on GCS between first medical contact and randomization
- DVT/PE in last 6 months or known hypercoagulable disorder
- STEMI
- NSTEMI
  - Either one of the following:
    - ECG changes c/w ischemia in a vascular distribution with chest pain in conscious patient OR
    - Troponin > 0.3 regardless of consciousness or chest pain

Estimated Sample Size – 750 patients in each arm

- Assumptions
  - 60% mRS 0-3 in placebo arm at six months
  - Effect size 7%
  - Binomial distribution, two-sided test, alpha=0.05, beta=0.2
  - Sample size may be reduced with higher proportion of "good outcome" in placebo arm using sliding dichotomy