

Management of Intracerebral Hemorrhage

Steven Messé, MD
Assistant Professor of Neurology
University of Pennsylvania Medical Center



What To Do With the Patient Once They Are Stabilized?

- BP management
- ICP management
- EVD placement and surgical evacuation
- Seizure prophylaxis and EEG monitoring



Blood Pressure Management



Blood Pressure In ICH

- Elevated BP is common in ICH
- “Chicken or the egg” problem
 - Does BP increase result from ICH? *Or*
 - Does BP increase cause ICH?



Blood Pressure In ICH

- Theoretically:
 - Lowering BP may decrease ongoing bleeding from ruptured small arteries (GOOD)
 - Lowering BP may decrease cerebral perfusion pressure, potentially affecting perihematomal penumbral tissue or fixed atherstenoses(BAD)



No Penumbra in ICH

- Multiple studies in animal and humans have failed to demonstrate an ischemic penumbra surrounding ICH (Qureshi, Neurology 1999; Diringer, Neurology 1998)
- No evidence of decrease in CBF with blood pressure lowering

Effect of pharmacologic blood pressure reduction in 14 patients with intracerebral hemorrhage (Powers, Neurology 2001)

Parameter	Baseline	Treated	<i>p</i> Value
Mean arterial pressure, mm Hg, mean \pm SD (range)	143 \pm 10 (129–158)	119 \pm 11 (90–133)	
Global CBF, mL 100 g ⁻¹ min ⁻¹ , mean \pm SD	32.1 \pm 7.1	31.5 \pm 8.4	0.490
Periclot CBF, mL 100 g ⁻¹ min ⁻¹ , mean \pm SD	18.9 \pm 9.7	18.1 \pm 8.8	0.402



BP Lowering in ICH: INTERACT Trial

- RCT of intensive BP lowering (goal reduction to SBP < 140 within 1 hour) vs standard practice (AHA guideline driven, SBP < 180)
- 404 patients in China/Australia/Korea
- Patients had baseline SBP > 150 and < 220
- Treatment started within 6 hours of onset
- CT at baseline and 24 hours

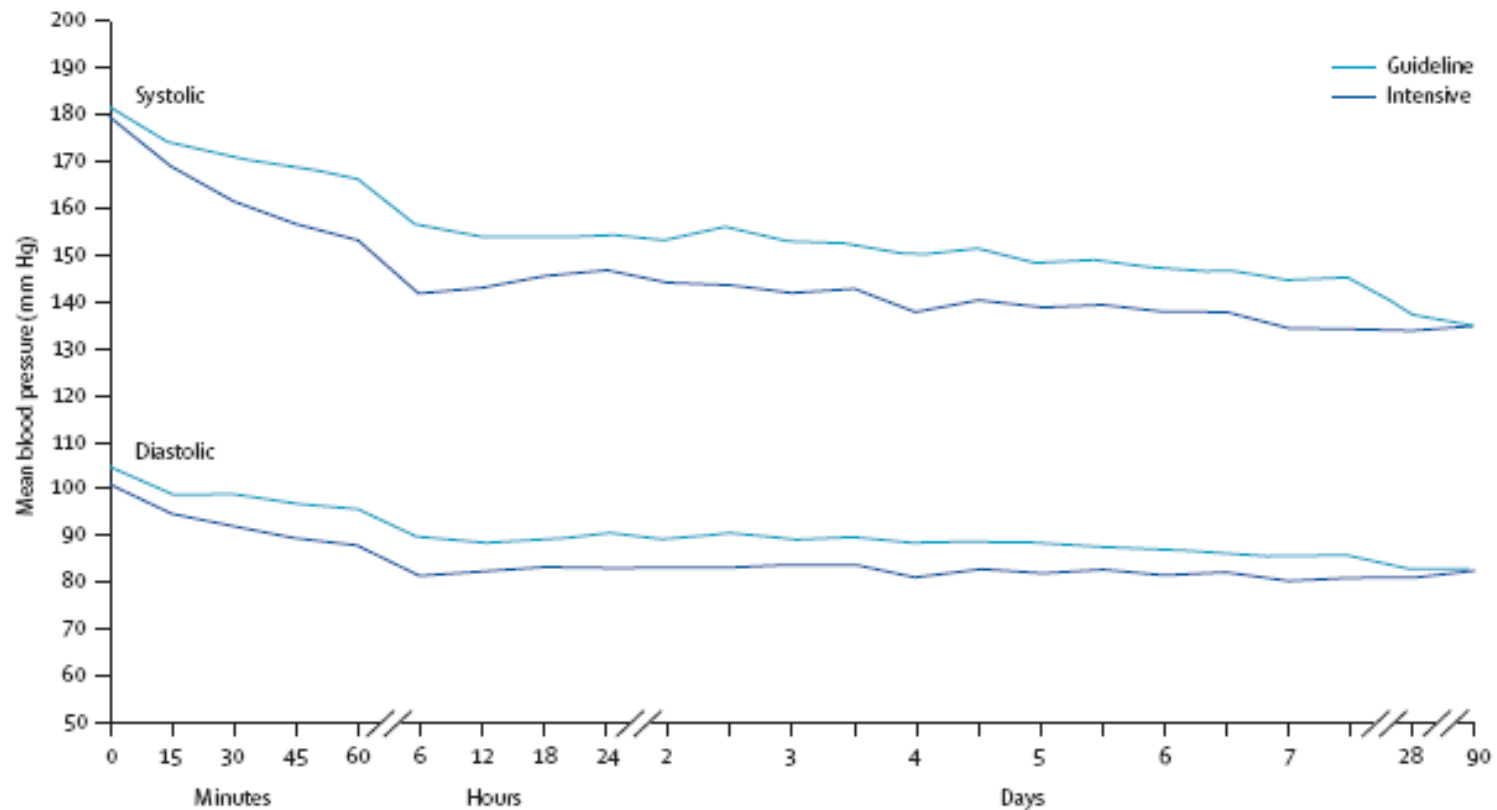


BP Lowering in ICH: INTERACT Trial

- Baseline characteristics of two groups similar except mean baseline ICH volume was greater in the intensive therapy group ($14.2 \pm 14.5\text{mL}$ vs $12.7 \pm 11.6\text{mL}$)
- Time to randomization (median) 3.4 hours in both groups
- GCS (median) 14 in both groups
- SBP was an average of 13 mmHg lower in intensive group within the first hour ($p < 0.0001$), 11 mmHg from 1-24 hours ($p < 0.0001$)



BP Lowering in ICH: INTERACT Trial



BP Lowering in ICH: INTERACT Trial

- Mean proportional hematoma growth was lower in intensive group (14% vs 36%, $p=0.06$) after adjustment for baseline ICH volume and time to CT
- Frequency of major ICH growth ($> 33\%$ or 12.5 ml) was 36% lower in intensive group (15% vs. 23%, $p=0.05$)
- Average of about 2 cc less ICH growth in intensive group
- No difference in adverse events or clinical outcome (death, disability, neurological deterioration)



AHA Guidelines 2010

Blood pressure management-ICH

Level of
evidence

C

- If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of BP with continuous intravenous infusion, with frequent BP monitoring every 5 min.
- If SBP is >180 mm Hg or MAP is >130 mm Hg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing BP using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure 60 mm Hg.
- If SBP is >180 mm Hg or MAP is >130 mm Hg and there is not evidence of elevated ICP, then consider a modest reduction of BP (eg, MAP of 110 mm Hg or target BP of 160/90 mm Hg) using intermittent or continuous intravenous medications to control BP and clinically reexamine the patient every 15 min.

B

- In patients presenting with a systolic BP of 150 to 220 mm Hg, acute lowering of systolic BP to 140 mm Hg is probably safe

Morgenstern et al. Stroke. 2010 Sep;41(9):2108-29



Blood Pressure Lowering: The Bottom Line

- Experimental data suggests BP lowering does not cause peri-hematoma ischemia
- Prospective RCT data demonstrated that an aggressive BP goal is safe and associated with less ICH expansion (but not improved outcomes)
- Enroll patients in ongoing trials (ATACH II, INTERACT II)
- Sensible to lower BP to a goal SBP ~140 – 160 depending on starting pressure
 - Monitor and maintain CPP if ICP is elevated



ICP Management



Possible Interventions for High ICP

- Treat edema/mass effect
 - Hyperventilation, steroids, glycerol, mannitol, hypertonic saline?
- Reduce ICH size directly
 - Surgery?

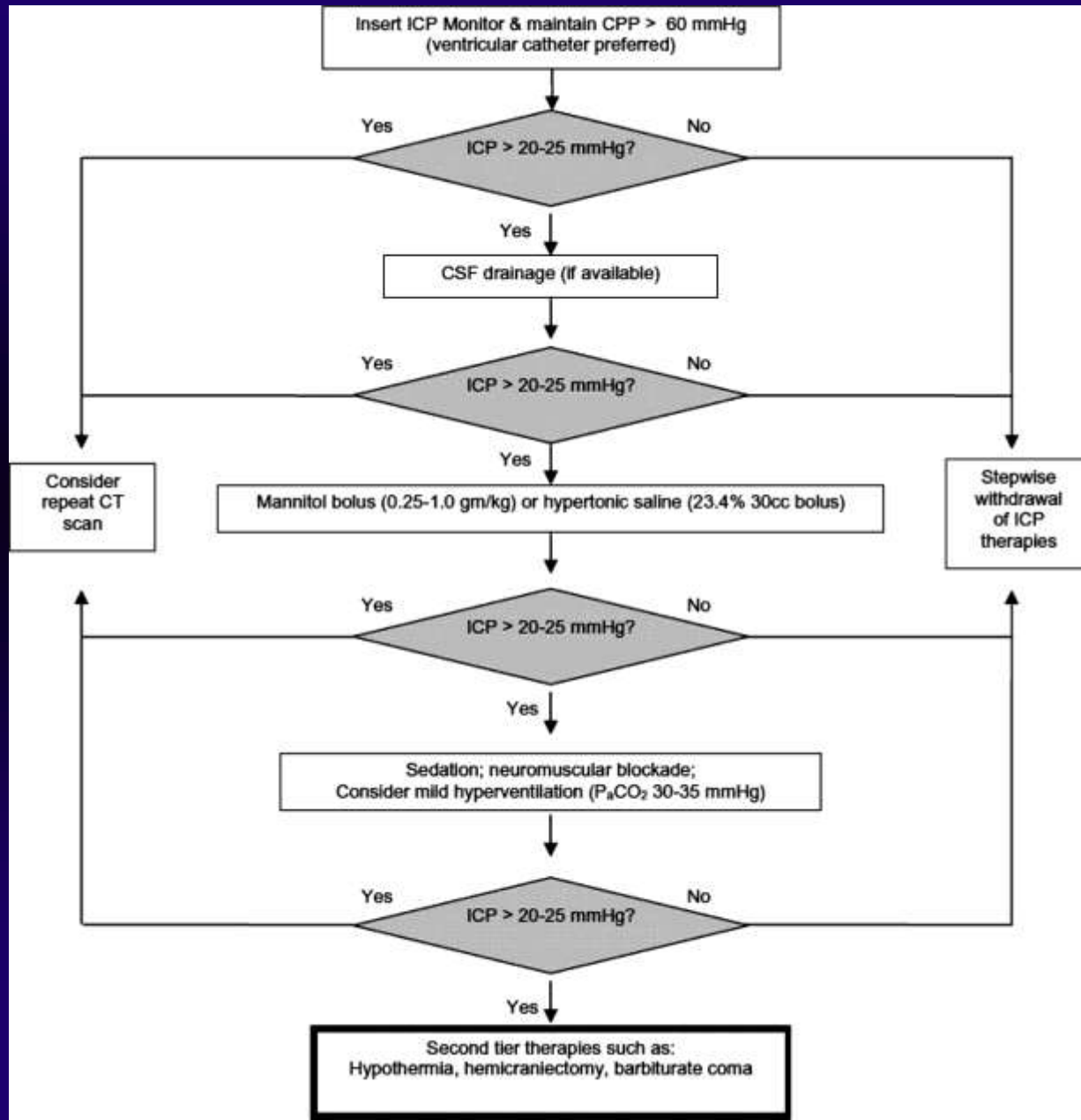


Edema and Mass Effect

- Hyperventilation provides a short lived effect and is generally only helpful as a bridging measure to definitive therapy
- Steroids and glycerol have been shown to be ineffective (with increased adverse events)
- Mannitol and hypertonic saline have limited evidence that they can reduce edema and temporarily reverse herniation
 - They are both reasonable to use but invasive ICP monitoring should be considered to guide therapy



AHA Guidelines 2010 – ICP Management



Reduce ICH Size Directly: Surgical Evacuation

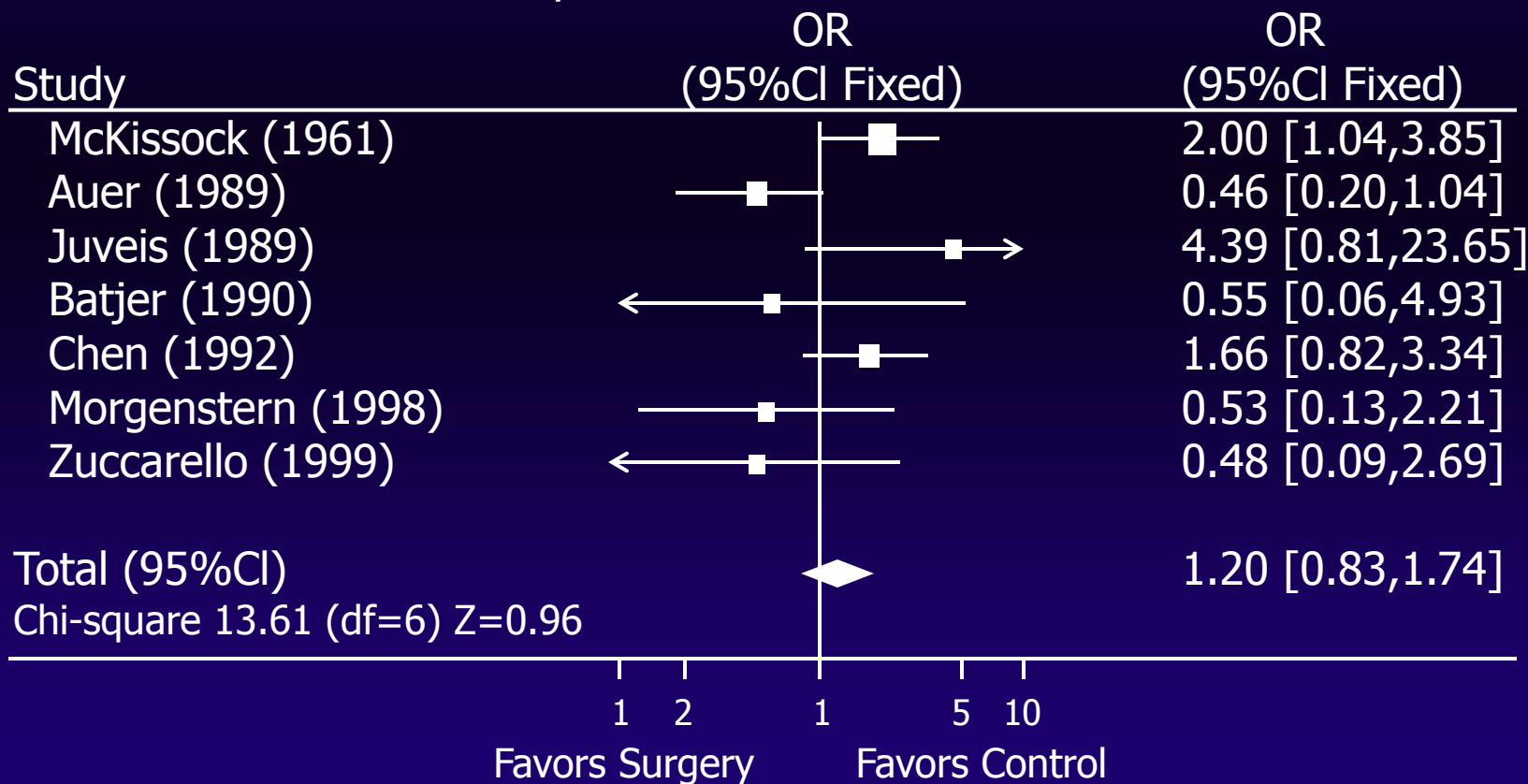


Meta-Analysis of Surgical Rx

Meta-analysis of 7 RCTs for surgical treatment of ICH shows no benefit

Comparison: surgery v control

Outcome: death or disability



“Ultra-Early” Surgery (< 4 hours)

- Surgical evacuation vs medical therapy
- Treatment < 4 hours from onset
- Study stopped after 11 patients treated surgically:
 - High rate of rebleeding (40%) in surgically treated patients
 - High mortality in those who rebled (75%)



Surgical Evacuation for Cerebellar Hemorrhage

- Comprises ~10% of ICH
- Non-randomized prospective study of 75 patients with cerebellar hemorrhage $> 40\text{mm}$ and $\text{GCS} < 13$
- Good outcome occurred in 58% with surgery and in 18% with conservative medical therapy
- Subsequent studies consistent
- EVD alone is not recommended



I-STICH

International-Surgical Treatment for Intracerebral Hemorrhage

- 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”
- Treatment < 72 hours from onset
 - median 30 hours, IQR 16-49 hours
- Patients with GCS ≥ 5
- Surgery via craniotomy 75%, stereotactic 25%



I-STICH: ICH Size/Location

International-Surgical Treatment for Intracerebral Hemorrhage

	Early surgery (n=503)	Initial conservative treatment (n=530)
Site of haematoma		
Lobar	196 (39%)	214 (40%)
Basal ganglia/thalamic	210 (42%)	224 (42%)
Both	94 (19%)	90 (17%)
Not assessable	3 (1%)	2
Left side of haematoma	265 (53%)	285 (54%)
Haematoma volume (mL)*	40 (24–63)	37 (23 – 60)
Minimum depth from cortical surface (cm)	1.0 (0.1–2.0)	1.0 (0.0–2.0)



I-STICH: Results

**International-Surgical Treatment for Intracerebral Hemorrhage
(Mendelow AD, Lancet 2005)**

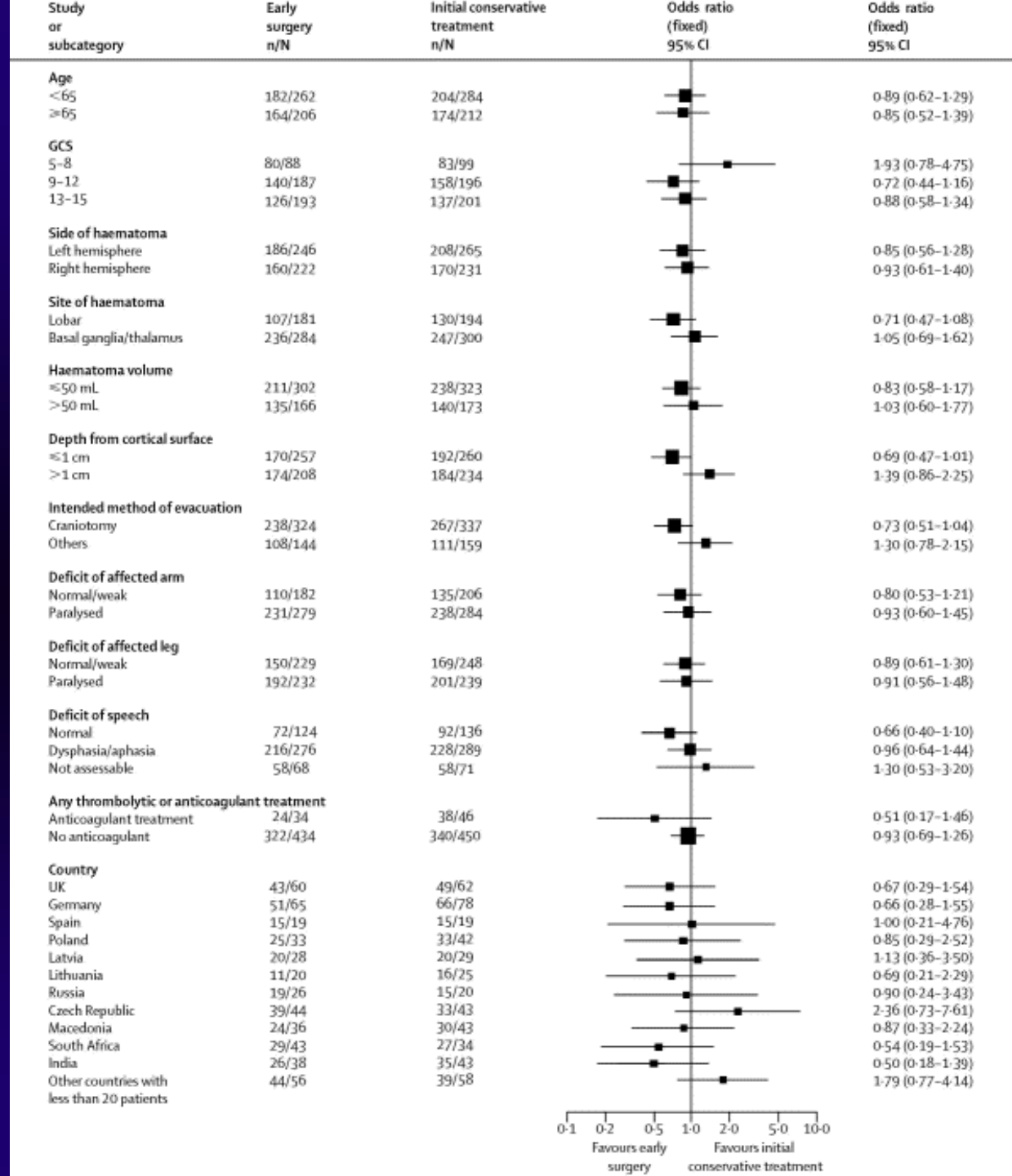
	Surgery	Medical	
Favorable	26.1%	23.8 %	OR 0.89 (0.66-1.18)
Mortality	36.3 %	37.1 %	

- Outcome determined by prognosis based GOS (taking into account age, admission GCS, and ICH volume)
- Analysis using Rankin and Barthel similar

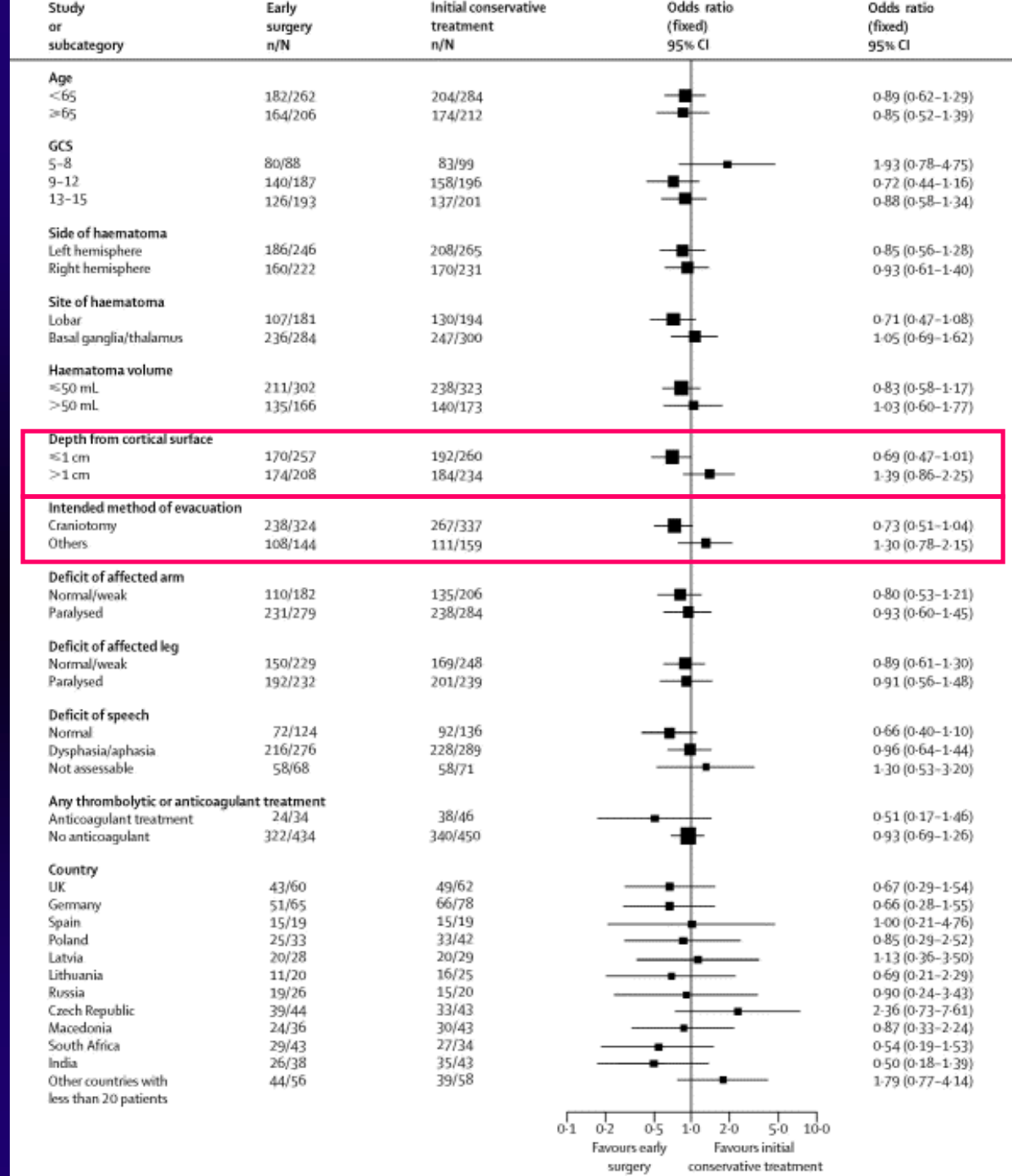


Prespecified subgroup analysis

(Mendelow AD, Lancet 2005)



Prespecified subgroup analysis



I-STICH Remaining Questions

- Were patients least likely to benefit the ones most likely to be enrolled?
- Is surgery at 30 hours after symptom onset “early” – or is it too late?
 - Subgroup analysis based on time to surgery?
- Should we believe subgroup analysis of bleed location?



AHA Guidelines 2010

Level of
evidence

B

- For most patients with ICH, the usefulness of surgery is uncertain with the following exceptions:
 - Patients with cerebellar hemorrhage who are deteriorating or have hydrocephalus should undergo evacuation as soon as possible. EVD alone is not recommended in these patients
 - For patients with lobar clots >30 mL and within 1 cm of the surface, evacuation might be considered
 - Minimally invasive clot evacuation is considered investigational
 - Very early craniotomy may be harmful due to increased risk of recurrent bleeding



Intraventricular Hemorrhage

- IVH may occur in isolation
- ICH is associated with IVH in ~ 45% of cases
- May result in hydrocephalus and increased ICP
- IVH portends a worse outcome



Ventriculostomy Drainage and IVH

- Never studied prospectively
- Generally associated with poor outcome
- Main risks are hemorrhage and infection
 - Infection risk related to duration of EVD
- Preliminary data suggests EVD + tPA improves clearance of IVH
 - CLEAR IVH: A randomized controlled trial of intraventricular tPA to expedite clearance of IVH and improve outcome
 - Prelim data: 1mg Q8h resulted in fewer VPS (22% vs 50%) and shorter LOS in ICU (7.5 vs 12)

Broderick J, et al. AHA Guidelines for the management of spontaneous intracerebral hemorrhage in adults. Circulation. 2007 Oct 16;116(16):e391-413.



Seizures in ICH



Seizures in ICH

- **Seizures are more frequent in ICH than in ischemic stroke**
- **Seizure risk ~8% in first few days after ICH**
- **Most seizures at onset or \leq 24 h of ICH**
- **More commonly associated with lobar than deep ICH**
- **Potential for worse outcomes**
 - Neuronal injury and destabilization of critically ill patient
 - Nonconvulsive seizures may contribute to coma
 - Seizures associated with deterioration of NIHSS and increased midline shift
 - However, no association with worse long term outcome after adjusting for other predictors

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.

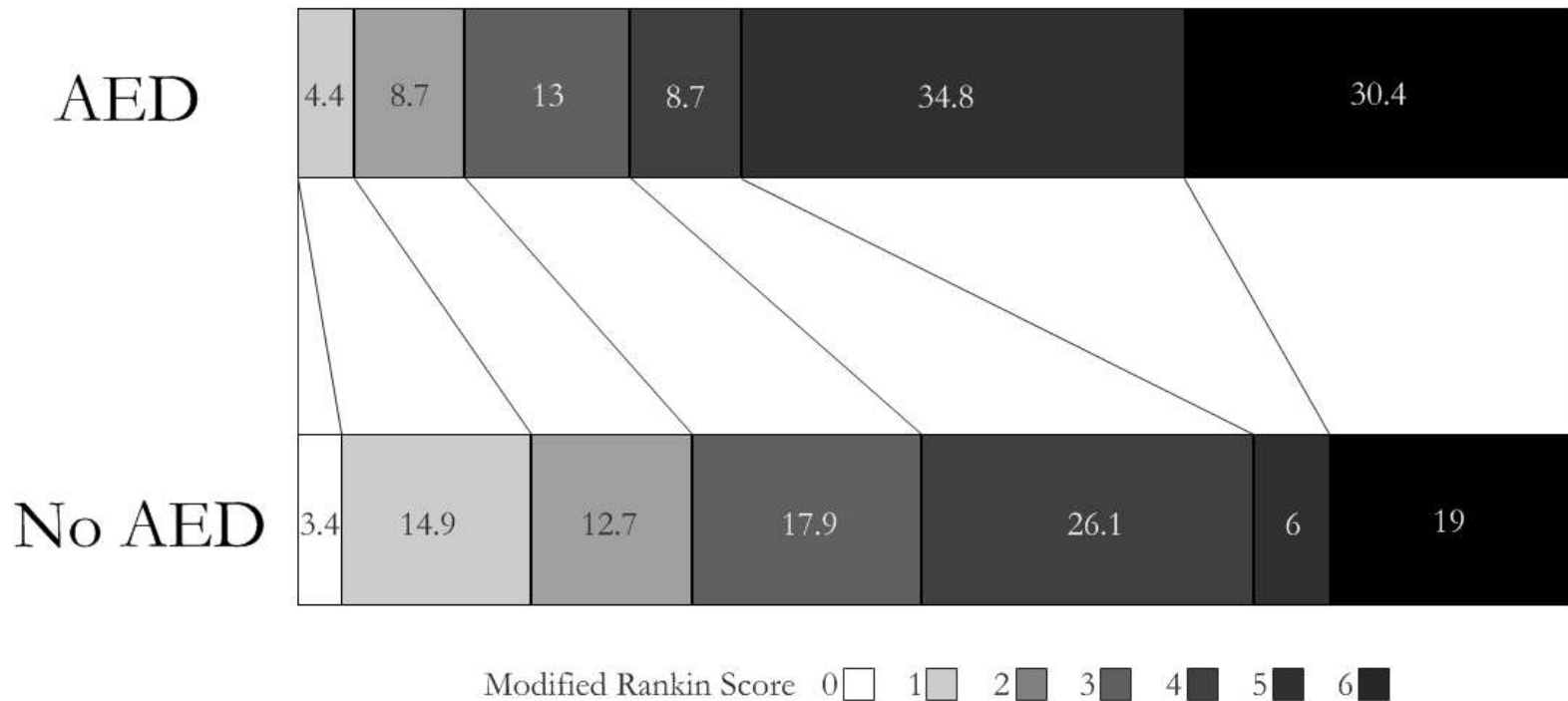


Prophylactic AEDs in ICH

- Cerebral Hemorrhage and NXY-059 Trial (CHANT)
 - RCT of a putative neuroprotectant
 - 303 patients received placebo
- 23 placebo patients (8%) were initiated on AEDs without documented seizure
- Initiation of AEDs was robustly associated with poor outcome (OR 6.8; 95%CI: 2.2-21.2, $p=0.001$) after adjustment for other known predictors of outcome after ICH (age, initial hematoma volume, presence of intraventricular blood, initial Glasgow Coma Score, and prior warfarin use)



Prophylactic AEDs in ICH



Prophylactic AEDs in ICH

- A second prospective cohort of 98 ICH patients
 - 7% had a seizure
- Phenytoin was associated with more fever and worse modified Rankin Scale at 3 months
- Levetiracetam use was not associated with any difference in outcome



AHA Guidelines *2010*

Seizures in ICH

Level of
evidence

- A** { • Clinical seizures should be treated with antiepileptic drugs
- B** { • Continuous EEG monitoring is probably indicated in ICH patients with depressed mental status out of proportion to the degree of brain injury
- C** { • Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiepileptic drugs
- B** { • Prophylactic anticonvulsant medication should not be used



Conclusions

- ICH remains a devastating disease
- No specific intervention has been demonstrated to improve outcomes
 - Aggressive supportive care is key
- Multiple promising treatment paradigms under investigation
 - Aggressive BP lowering
 - EVD +tPA for IVH
 - Factor VIIa in select patients
 - Neuroprotection?



Questions?

