Controversies in the Management of SAH

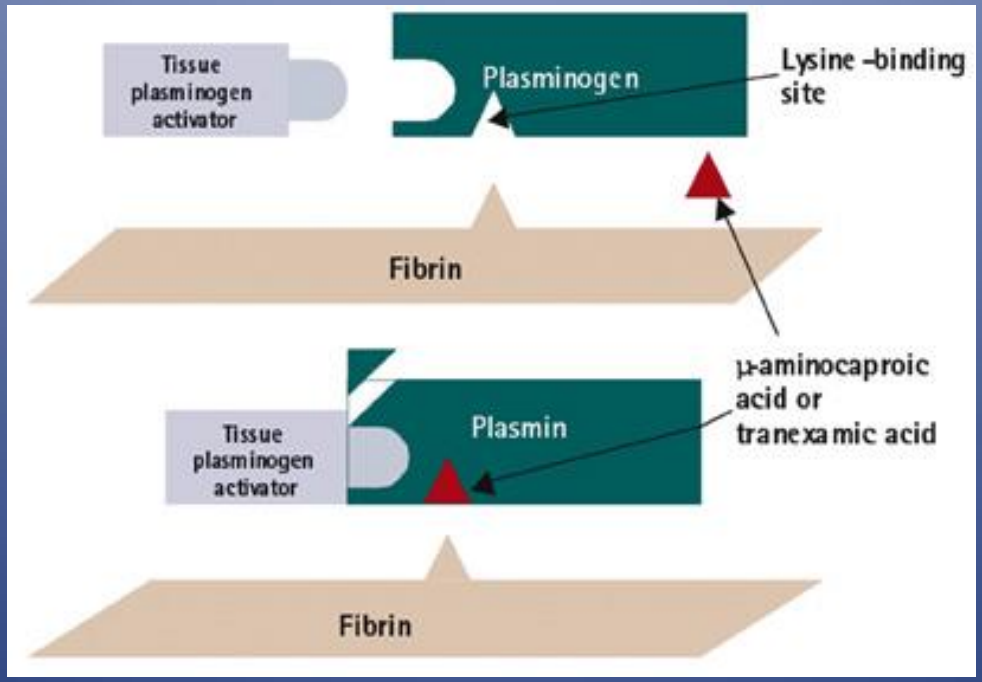
Disclosures: None

Controversies

- Anti-fibrinolytics
- Anti-epileptic Drugs
- Goal Hemoglobin
- Hyponatremia
- Fever

Anti-Fibrinolytics

- The risk of re-bleeding is highest in the first 24 hours after SAH (highest about 6 hours after)
- The prognosis after re-bleeding is poor. It is estimated that approximately 60% of people who re-bleed die



Antifibrinolytic effect of tranexamic acid. *British Dental Journal* **198**, 33 - 38 (2005)

Anti-Firinolytics

- There have been 10 randomized studies using TXA or EACA with 1904 participants since 1978.

- In the six trials that reported cerebral ischemia rates, anti-fibrinolytic treatment significantly increased the risk of cerebral ischemia (RR 1.41, 95% CI 1.04 to 1.91; 83 per 1000 people

Fodstad H, Forssell A, Liliequist B, Schannong M. Antifibrinolysis with tranexamic acid in aneurysmal subarachnoid hemorrhage: a consecutive controlled clinical trial. *Neurosurgery* 1981;**8**:158-65

Girvin JP. The use of antifibrinolytic agents in the preoperative treatment of ruptured intracranial aneurysms. *Transactions of the American Neurological Association* 1973;**98**:150-2

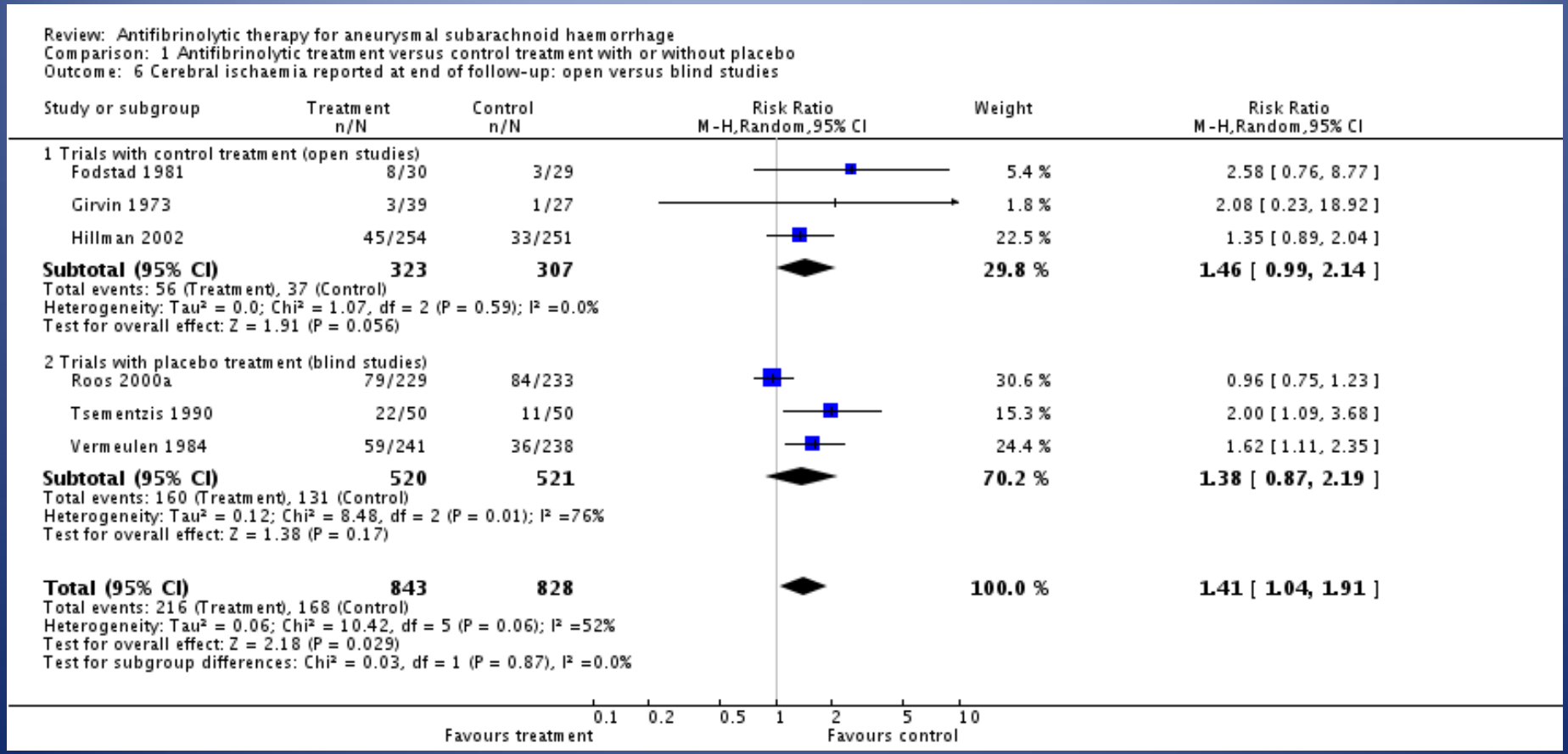
Roos Y, for the STAR-study group. Antifibrinolytic treatment in aneurysmal subarachnoid haemorrhage: a randomized placebo-controlled trial. *Neurology* 2000;**54**:77-82. [

Tsementzis SA, Hitchcock ER, Meyer CH. Benefits and risks of antifibrinolytic therapy in the management of ruptured intracranial aneurysms. A double-blind placebo-controlled study. *Acta Neurochirurgica* 1990;**102**:1-10.

Vermeulen M, Lindsay KW, Murray GD, Cheah F, Hijdra A, Muizelaar JP, et al. Antifibrinolytic treatment in subarachnoid hemorrhage.*New England Journal of Medicine* 1984;**311**:432-7.

Hillman J, Fridriksson S, Nillson O, Yu Z, Saveland H, Jakobsson KE. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study

Anti-Fibrinolytics



Baharoglu MI, Germans MR, Rinkel GJ. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2013 Aug 30;8:CD001245.

Anti-Fibrinolytics

- Last RCT using tranexamic acid was in 2002.
- Tranexamic acid was given until aneurysm occlusion or up to 72 hours after SAH
- A reduction in the re-bleeding rate from 10.8% to 2.4% was seen which correlated with a favorable outcome increase according to the GOS increased from 71 to 75%.
- According to TCD measurements and clinical findings, there were no indications of increased risk of either ischemic clinical manifestations or vasospasm that could be linked to tranexamic acid treatment.

Hillman J, Fridriksson S, Nilsson O. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. J Neurosurg. 2002 Oct;97(4):771-8.

Anti-Fibrinolytic

- Furthermore , a case control study looking at 73 patients who received EACA for up to 72 hours.
- There was no difference in ischemic complications between cohorts.
- There was a significant 8-fold increase in deep venous thrombosis in the EACA group but no increase in pulmonary embolism.
- There was a nonsignificant 76% reduction in mortality attributable to rebleeding.

Starke RM, **Impact of a Protocol for Acute Antifibrinolytic Therapy on Aneurysm Rebleeding After Subarachnoid Hemorrhage**. Stroke, 2008

Anti-Fibrinolytics

- Another large concern with antifibrinolytics has been thromboembolic events.
- Two large studies in trauma have not documented a difference in thromboembolic events. (MATTERS, CRASH-2)
- A systematic review of 57 studies with any anti-fibrinolytic drug confirmed that the frequencies of DVT or PE were low at 1.9% for TXA

Ross J1, Al-Shahi Salman R. The frequency of thrombotic events among adults given antifibrinolytic drugs for spontaneous bleeding: systematic review and meta-analysis of observational studies and randomized trials. Curr Drug Saf. 2012 Feb;7(1):44-54.

Anti-Fibrinolytics

- Another concern with anti-fibrinolytics has been seizures.
- In 2010, TXA started being used during cardiac surgery.. While patients didn't have new ischemic injury, they were having increased postoperative convulsive seizures from 1.3% to 3.8%.
- Patients received high doses of TXA intraoperatively ranging from 61 to 259 mg/kg.
- This study was later confirmed by large multi-variate analyses.

Murkin JM1, Falter F, Granton J. High-dose tranexamic Acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg. 2010 Feb 1;110(2):350-3.

Sharma V. The association between tranexamic acid and convulsive seizures after cardiac surgery: a multivariate analysis in 11 529 patients. Anaesthesia. 2014 Feb;69(2):124-30

Anti-Fibrinolytics

- 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)***.

Anti-convulsants in SAH

- Timing of seizures: 10 to 15% of patients have seizures at ictus
- 1-2% have seizures before aneurysm is secured
- 2-10% have in hospital seizures before discharge (on AEDs).

Lin CL. Characterization of perioperative seizures and epilepsy following aneurysmal subarachnoid hemorrhage. JNS 2003

Seizure Prophylaxis

- Numerous retrospective studies have highlighted patients at higher risk for seizures:
  - aneurysms in the MCA
  - thick aSAH
  - Poor neurologic grade

  - In respect to poor-grade aneurysmal comatose patients with a Glasgow Coma Scale of ≤8, the risk of seizures might be higher. They have a 10% risk of non convulsive seizures based on scalp electrodes

Claassen J. Nonconvulsive seizures after SAH: multimodal detection and outcomes. Ann Neurol. 2013 Jul; 74(1): 53–64.
Little AS. Nonconvulsive status epilepticus in patients suffering spontaneous subarachnoid hemorrhage. J Neurosurg. 2007; 106: 805–811.
Choi, Seizures and epilepsy following aneurysmal subarachnoid hemorrhage: incidence and risk factors. J Korean Neurosurg Soc. 2009; 46: 93–98.

Seizure Prophylaxis

- Numerous retrospective studies have shown an association between AED prophylaxis and worse outcome, vasospasm, and cerebral infarction.
- Some studies have shown higher phenytion dosages correlate with worse outcomes. Again association.
- A few have shown that even after correcting for other factors, AEDs still trend towards giving a worse prognosis

- The potential risks and benefits of newer generation AEDs are unknown and a potential topic for further studies

Rosengart A. Outcom in patietns with SAH treated with antiepileptic drugs . JNS. August 2007:107

Naidech AM. Phenytoin Exposure Is Associated With Functional and Cognitive Disability After Subarachnoid Hemorrhage. Stroke. 2005 Mar;36(3):583-7

Duration of AED

- There are 2 retrospective studies with spontaneous SAH showing a 3 days course was adequate.

- In patients suffering a seizure during hospitalization, the literature describes continuation of AED therapy for a variable period (6 weeks to 6 months).

Chumnanvej S, Dunn IF, Kim DH. Three-day phenytoin prophylaxis is adequate after subarachnoid hemorrhage. Neurosurgery. 2007;60:99–102

Baker CJ, Prestigiacomo CJ, Solomon RA: Short-term perioperative anticonvulsant prophylaxis for the surgical treatment of low-risk patients with intracranial aneurysms. Neurosurgery 37:863–870, 1995.

Anti-Convulsants in SAH

- The use of prophylactic anticonvulsants may be considered in the immediate posthemorrhagic period ***(Class IIb; Level of Evidence B)***.
- This may be changed for patients who look very good (thin cisternal blood with aneursym secured by coiling) or very ill

Hemoglobin in SAH

- Numerous retrospective studies have shown higher Hgb are associated with better outcome even after correcting for other large co-morbidities

- There are a handful of retrospective studies showing that transfusion is associated with medical complications.

Levine J. Red Blood Cell Transfusion Is Associated With Infection and Extracerebral Complications After Subarachnoid Hemorrhage
Smith MJ. Blood transfusion and increased risk for vasospasm and poor outcome after subarachnoid hemorrhage. JNS 2004

Goal Hemoglobin

- One randomized trial used a goal Hgb of 11.5 in 44 patients.
- The number of cerebral infarctions on MRI (6 vs. 9), NIH Stroke Scale scores at 14 days [1 vs. 2], and rates of independence on the mRS at 14 days (65% vs. 44%) and 28 days (80% vs. 67%) were similar, but favored higher goal HGB.

Naidech AM. Prospective, Randomized Trial of Higher Goal Hemoglobin after Subarachnoid Hemorrhage

Hgb Goals

- Sepsis
- Acute MI
- Non-cardiac surgery
- Cardiac Surgery

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The Implications of Bloc Transfusions for Patients

The NEW ENGLAND JOURNAL of MEDICINE

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Liberal or Restrictive Transfusion after Cardiac Surgery

Gavin J. Murphy, F.R.C.S., Katie Pike, M.Sc., Chris A. Rogers, Ph.D., Sarah Wordsworth, Ph.D., Elizabeth A. Stokes, M.Sc.,

The NEW ENGLAND JOURNAL of MEDICINE

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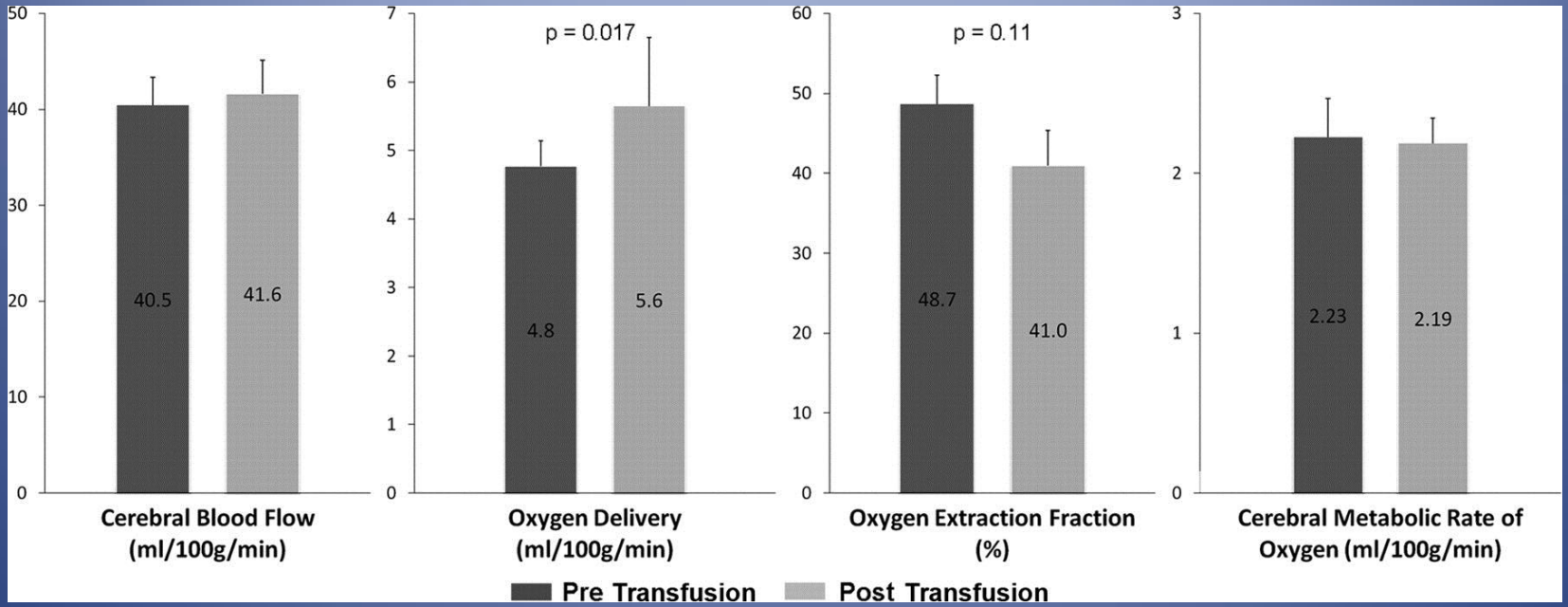
Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

Lars B. Holst, M.D., Nicolai Haase, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Jan Wernerman, M.D., Ph.D.,

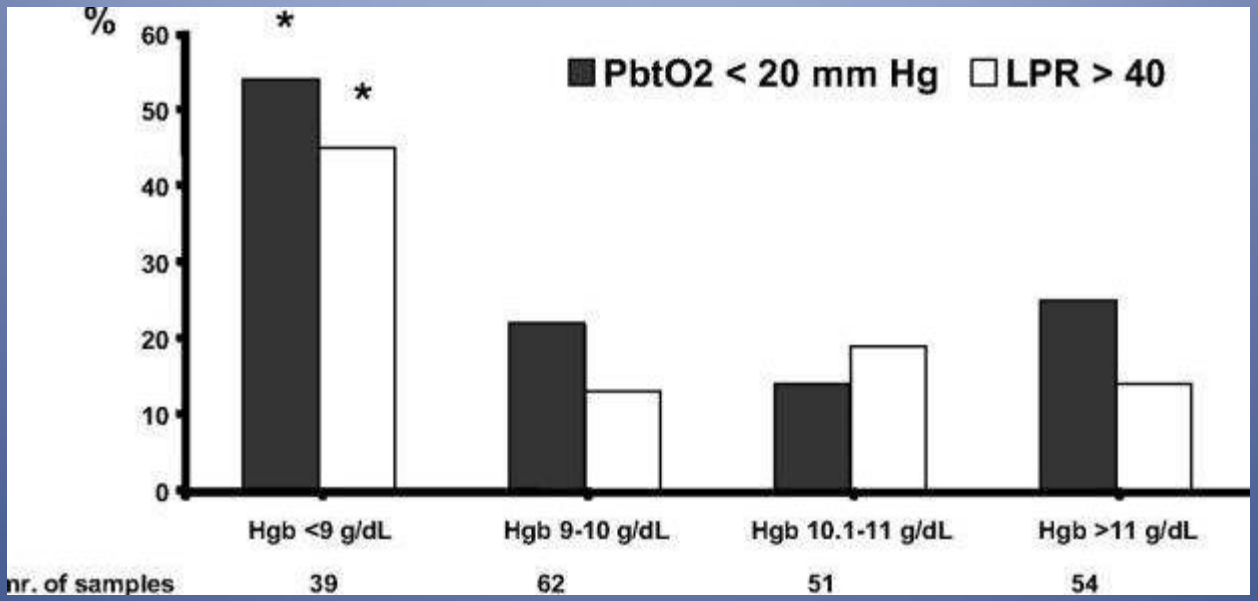
Hemoglobin



On a metabolic level, transfusion increases DO2 but causes a compensatory fall in oxygen extraction fraction

Dhar R. Red blood cell transfusion increases cerebral oxygen delivery in anemic patients with subarachnoid hemorrhage. Stroke 2009

Hemoglobin



In poor grade SAH patients, patients with lower Hgb spent more time with oxygen tensions less than 20 and LPR less than 40

Odd et al, Hemoglobin concentration and cerebral metabolism in patients with aneurysmal subarachnoid hemorrhage. 2009

Hemoglobin

- The use of packed red blood cell transfusion to treat anemia might be reasonable in patients with aSAH who are at risk of cerebral ischemia. The optimal hemoglobin goal is still to be determined ***(Class IIb; Level of Evidence B)***. (New recommendation)

Hyponatremia

- Hyponatremia is seen in about 1/3 of patients
  - -50% of patinets with Acomm
  - -33% of patients with MCA an d PCA
  - 27% of apteints with ICA
- Multiple observational studies have shown it is associated with a worse outcome
- It is likely associated with confusion, seizures, and lethargy

Marupudi N, Diagnosis and Management of Hyponatremia in Patients with Aneurysmal Subarachnoid Hemorrhage. J Clin Med. 2015 Apr; 4(4): 756–767.

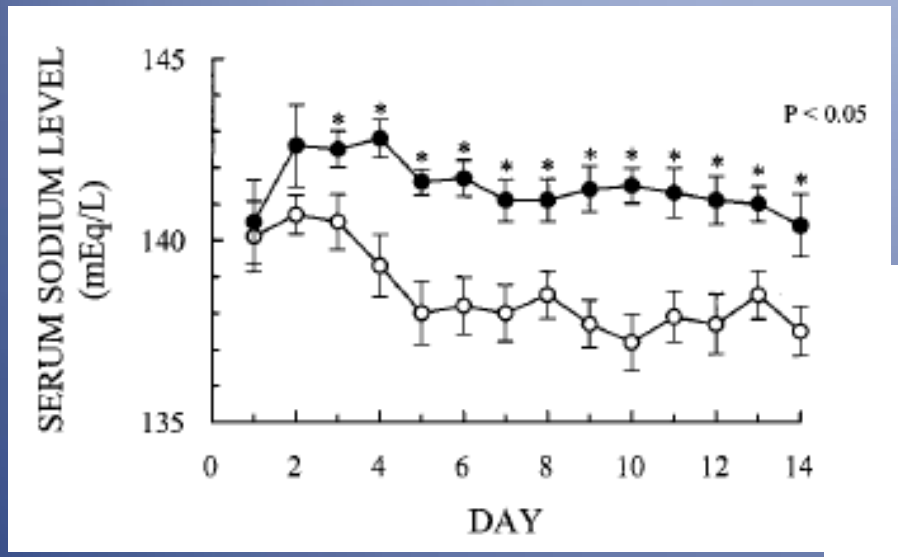
Hyponatremia

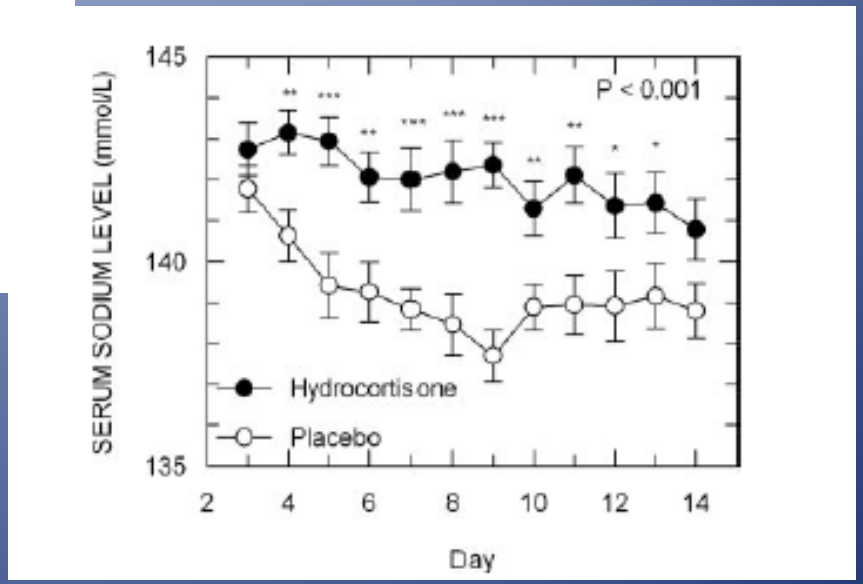
- SIADH
  - Hypo osmolality, renal excretion of Na (~40), high urine Osm (~100) and euvolemia
- Cerebral Salt Wasting
  - the definition is a diagnosis of exclusion
  - renal loss of sodium and chloride (not K) with concomitant

Biochemical marker	SIADH	CSW
Extracellular fluid volume	Normal to high	Low
Urinary sodium level	>40 mEq/L	>40 mEq/L
Serum uric acid level	Low	Low
Initial fractional excretion of urate	High	High
Fractional excretion of urate after correction	Normal	High
Urinary osmolality	High	High
Serum osmolality	Low	Low
Blood urea nitrogen/creatinine level	Low to normal	High
Serum potassium level	Normal	Normal to high
Central venous pressure	Normal to high	Low
Pulmonary capillary wedge pressure	Normal to high	Low
Brain natriuretic peptide level	Normal	High
Treatment	Water restriction	Fluids and/or mineralocorticoids

CSW = cerebral salt wasting; SIADH = syndrome of inappropriate antidiuretic hormone.

Hydrocortisone

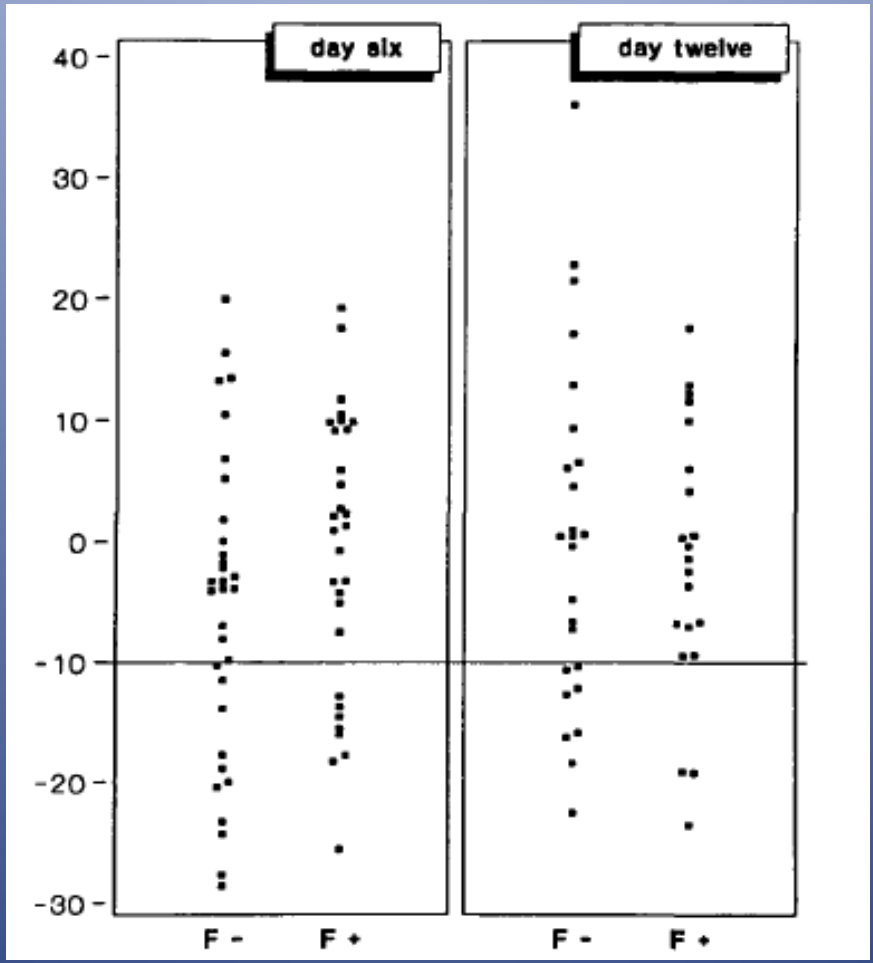




Moro N, Prophylactic Management of Evcessive Naturesis with Hydrocortisone for Efficient Hypervolemic Therapy after SAH Stroke 2003

Katayama Y, A RCT of Hydrocortisone Against Hyponatremia in Patients with SAH Stroke Aug 2007

Fludrocortisone



Hasan D. Effect of Fludrocortisone in Patients with SAH. Stroke. 1989

Fludrocortisone

- In another RCT with fludrocortisone in 30 patients. Fludrocortisone reduced the mean sodium and water intake levels from 634mEq and 6.6L to 487mEq and 5.2L

Hyponatremia

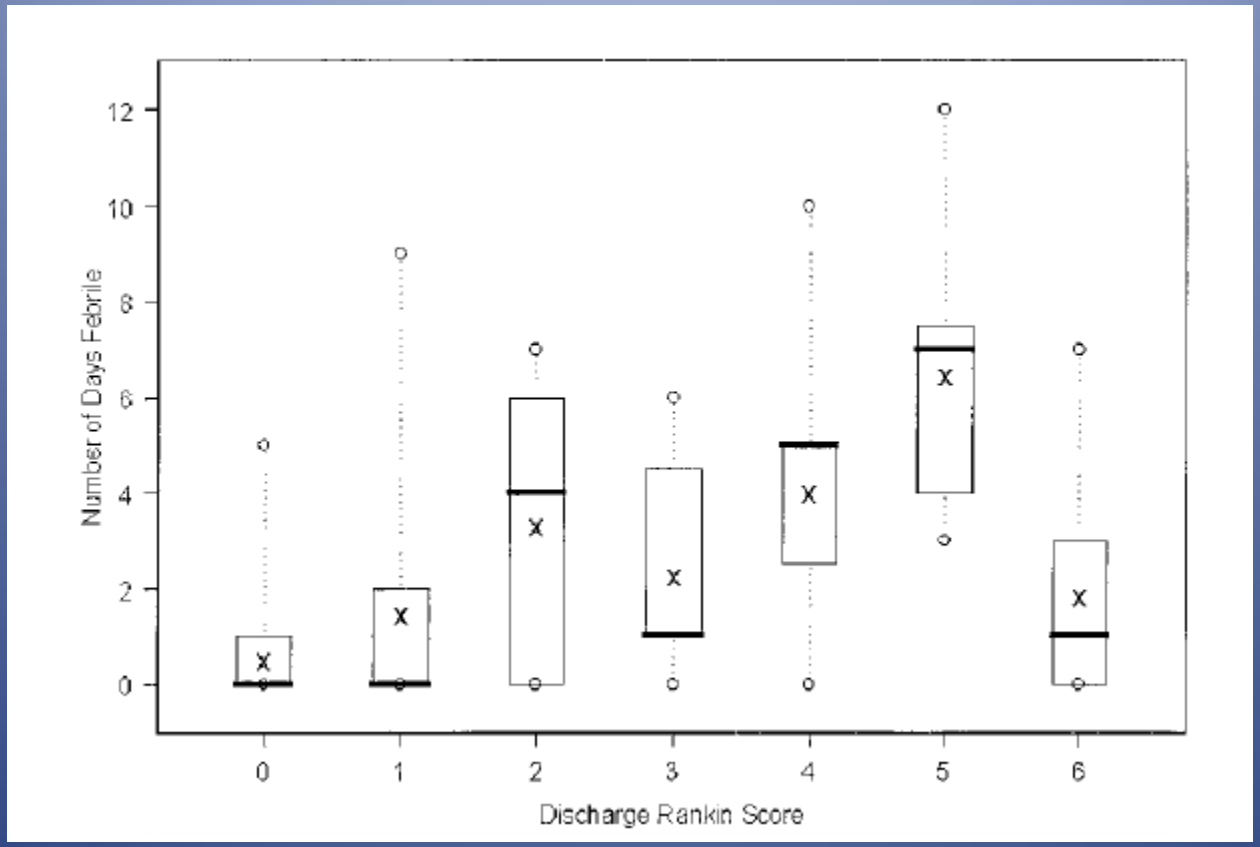
- The use of fludrocortisone acetate and hypertonic saline solution is reasonable for preventing and correcting hyponatremia ***(Class IIa; Level of Evidence B)***.

Fever Control

- Relationship between fever and well known with stroke patients
  - 1 degree increases the risk of poor outcome by 2x
- Interventricular blood is known to be a strong cause of fever
- Symptomatic VSP increases the risk of fever for 5x

Dorhout. Fever After Aneurysmal Subarachnoid Hemorrhage Relation With Extent of Hydrocephalus and Amount of Extravasated Blood

Fever



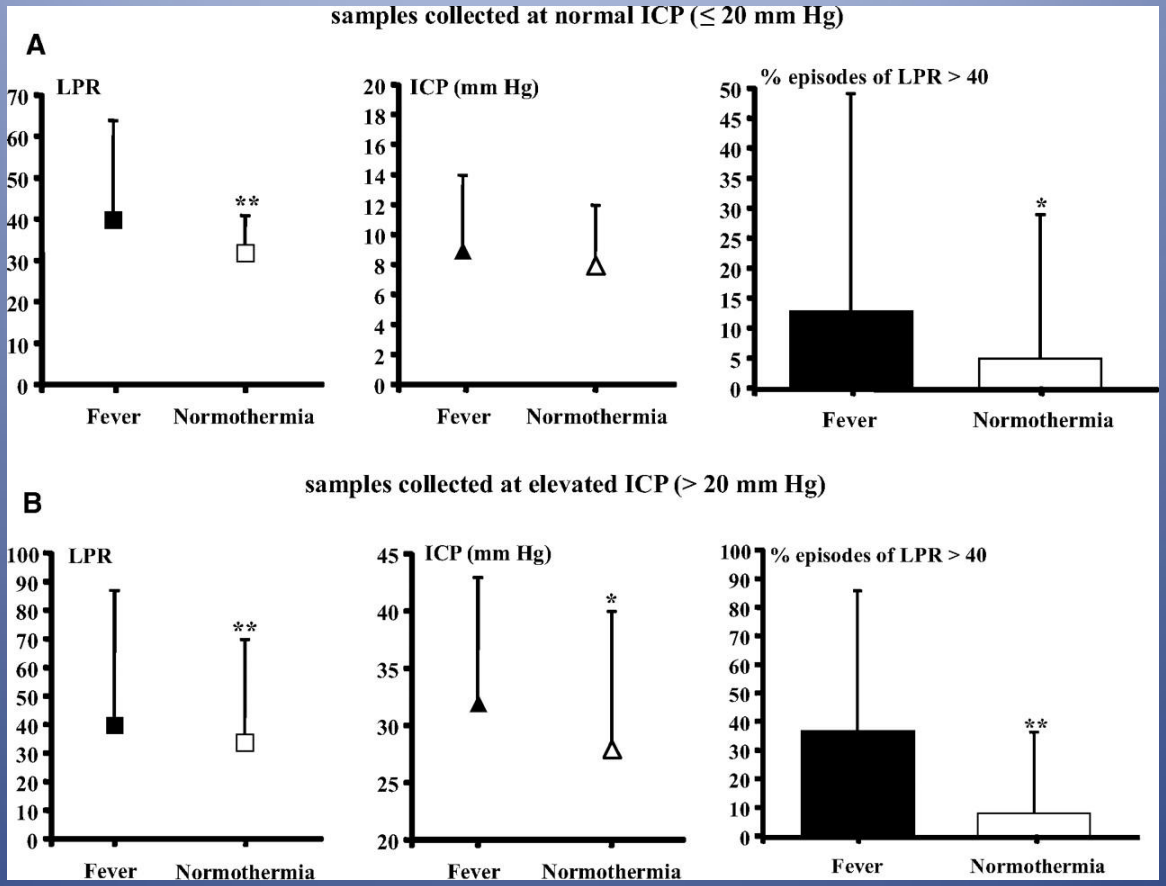
Oliveira-Filho J. Fever in subarachnoid hemorrhage Relationship to vasospasm and outcome.

Fever

- Average daily max temperature is associated with
  - an increased risk of death or severe disability (OR 3.0 per °C, 95% CI 1.6 to 5.8)
  - loss of independence in IADLs (OR 2.6, 95% CI 1.2 to 5.6),
  - cognitive impairment (OR 2.5, 95% CI 1.2 to 5.1, all $p \leq 0.02$).

Fernandez, A. Fever after subarachnoid hemorrhage Risk factors and impact on outcome

Fever



Oddo et al. Induced Normothermia attentuates cerebral metabolic distress in patients with aneurysmal SAH and refractory fever. Stroke 2009.

Fever

- There was a retrospective case control study looking at 40 patients with SAH who had a surface cooling device on admission compared to those who didn't.
- After matching by age, Hunt and Hess grade, and SAH sume score, those with the surface cooling device had a lower risk for poor outcome.

- No randomized trials in SAH for fever control and outcome

Bhadjatia, N. Impact of Induced Normothermia on Outcome After Subarachnoid Hemorrhage: A Case-Control Study. Neurosurgery April 2010.

Fever

Table 5 Multivariate logistic analysis for 28-day mortality in patients with lowest body temperature > 35°C

	Patients with sepsis (*N* = 507)		Patients without sepsis (*N* = 715)	
	Adjusted odds ratio (95% CI)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
Age (y.o., IQR)	1.02 (1.00, 1.03)	0.08	1.01 (0.98, 1.05)	0.52
APACHE (IQR)	1.07 (1.03, 1.11)	< 0.001	1.20 (1.11, 1.30)	< 0.001
Postoperative admission n (%)	0.79 (0.32, 1.91)	0.59	0.57 (0.21, 1.52)	0.26
Mechanical ventilation requirement n (%)	1.76 (0.98, 3.14)	0.06	3.49 (1.14, 10.7)	0.03
Cardiac or vascular diseases	0.85 (0.39, 1.82)	0.67	0.73 (0.24, 2.21)	0.57
Thoracic or respiratory diseases	1.23 (0.66, 2.28)	0.51	1.24 (0.40, 3.78)	0.71
MAX_{ICU}				
37.5°C to 38.4°C (vs. 36.5°C to 37.4°C)	0.42 (0.20, 0.88)	0.02	3.18 (0.78, 12.9)	0.11
38.5°C to 39.4°C (vs. 36.5°C to 37.4°C)	0.60 (0.25, 1.43)	0.25	7.49 (1.47, 38.1)	0.02
≥ 39.5°C (vs. 36.5°C to 37.4°C)	0.59 (0.21, 1.68)	0.32	11.7 (1.58, 87.0)	0.02
NSAIDs	2.48 (1.02, 6.01)	0.04	0.26 (0.032, 2.19)	0.22
Acetaminophen	1.95 (1.06, 3.57)	0.03	0.61 (0.23, 1.61)	0.32
Cooling	1.23 (0.69, 2.21)	0.47	1.26 (0.14, 11.0)	0.84

APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidential interval; MAX_{ICU}, maximum body temperature during an ICU stay; NSAIDs, non-steroid anti-inflammatory drugs

FACE Study Group. Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis. Critical Care 2012.

Fever

- Aggressive control of fever to a target of normothermia by use of standard or advanced temperature modulating systems is reasonable in the acute phase of aSAH ***(Class IIa; Level of Evidence B)***.