STRATEGIES IN THE MANAGEMENT OF VASOSPASM
THE TRIBULATIONS OF SAH TRIALS

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Introduction

- SAH remains associated with high mortality rate
- After impact of bleed and rebleeding, delayed cerebral ischemia from vasospasm is the leading cause of morbidity and mortality after SAH
- Typically starting post-bleed day 3 and peak incidence post-bleed day 7
- 20 to 30% of patients experience clinical symptoms and/or infarction

Kassell NF, J Neurosurg. 1990;73:18 –36.

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Introduction

Prognostic determinants of SAH outcome are:

- Neurological grade on initial examination,
- Volume of subarachnoid blood on initial computerized tomography (CT)
- Age
- Preexisting hypertension,
- Re-bleeding
- Delayed vasospasm

Kassell NF, J Neurosurg. 1990;73:18 –36.

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Classification of Strategies

- **Detection**
  - CT angiogram / perfusion
  - TCD
- **Prevention**
  - Statins
  - Magnesium
  - Erythropoietin
  - Endothelin Receptor Antagonists
  - Nicardipine
- **Palliation**
  - IA therapy (magnesium, nicardipine, verapamil, milrinone)
  - Cardiac performance
  - IT nicardipine/magnesium

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Vasospasm Detection

- Angiographic spasm occurs in over 50-70% of all patients, but is not always associated with morbidity.

- Symptoms remain the most important indicator of meaningful vasospasm

- TCD is limited:
    - Specificity/Positive Predictive Value
    - Technical difficulties limit usefulness

- What to do in cases when exam limited?
  - Routine angiogram at day 7 – 10 may be too late





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Vasospasm Detection

CT angiography

- Allows for non invasive assessment of vessels
- Advantageous in patients with poor exam/high risk for angio
- **Most reliable for either no spasm or severe spasm and in proximal vessels more than distal vessels.**

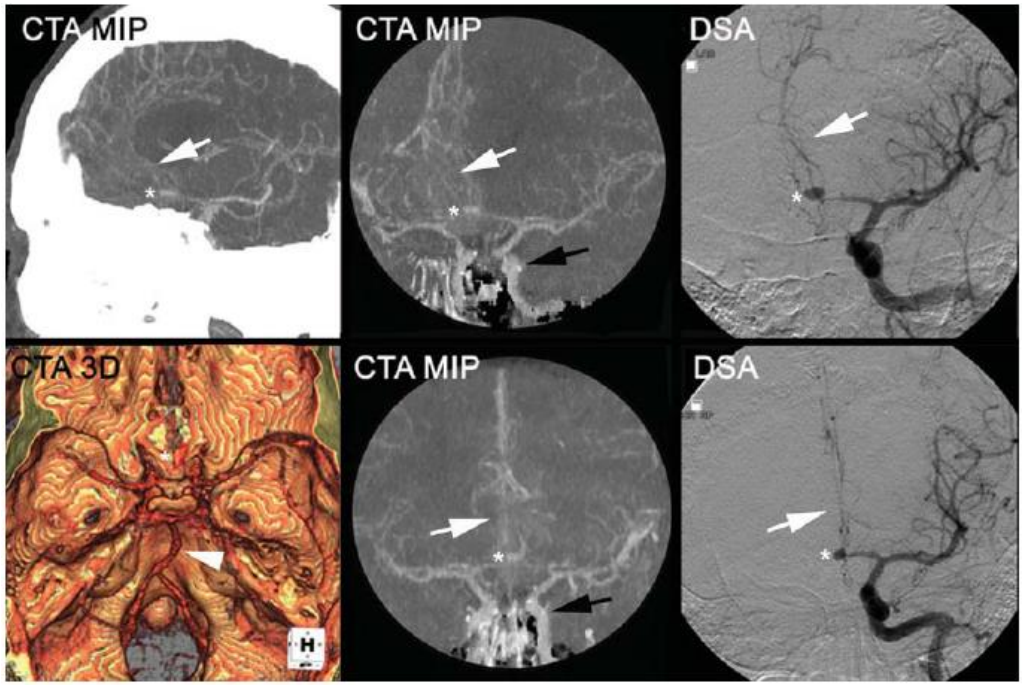


Table 3. Comparison of CTA to DSA for the diagnosis of vasospastic segments

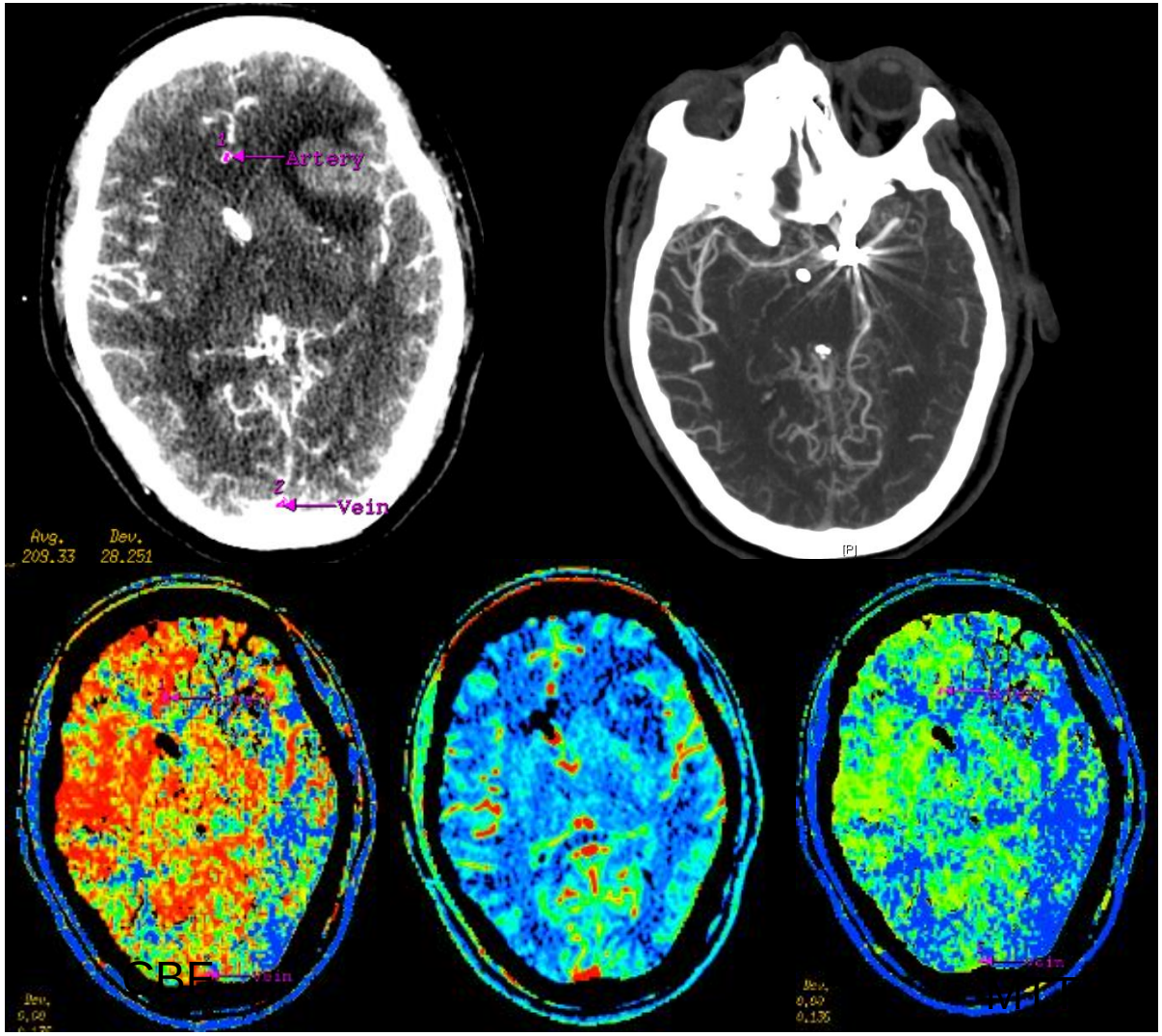
	Overall	Basilar	Vertebral artery	P1	P2	PCom	M1	M2	A1	A2	SICA
Sensitivity	63	100	100	67	50	50	58	60	77	72	45
Specificity	90	92	93	94	90	99	89	90	81	77	94
Accuracy	87	93	93	93	88	96	85	87	80	76	88
PPV	43	40	17	29	20	NA	46	50	45	48	63
NPV	95	100	100	99	97	97	94	94	95	90	91

Chaudhary et al. Cerebrovascular Dis. 2008;25(1-2):144-50.

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CT Perfusion Case Study

- 45 yo woman presented with HH4 F 3 SAH due to L MCA aneurysm.
- Underwent clipping PBD 1
- Post Op TCDs "limited" due to poor windows on right and clip artifact on left
- Underwent CT A/Perfusion on PBD 5 (asymptomatic…..poor exam)



CT Perfusion

Benefits

- Allows for assessment of the impact of spastic vessels on tissue:
- Typical picture of relevant spasm (poor exam):
  - CBF: reduced
  - MTT: increased (>8 sec)
  - CBV: increased (reduced at very last step)

Limitations

Practical

- An 18-gauge peripheral line
- 50-ml dose of iodinated contrast agent
- Dependent on adequate delivery of the contrast bolus (CHF, afib)

Technical

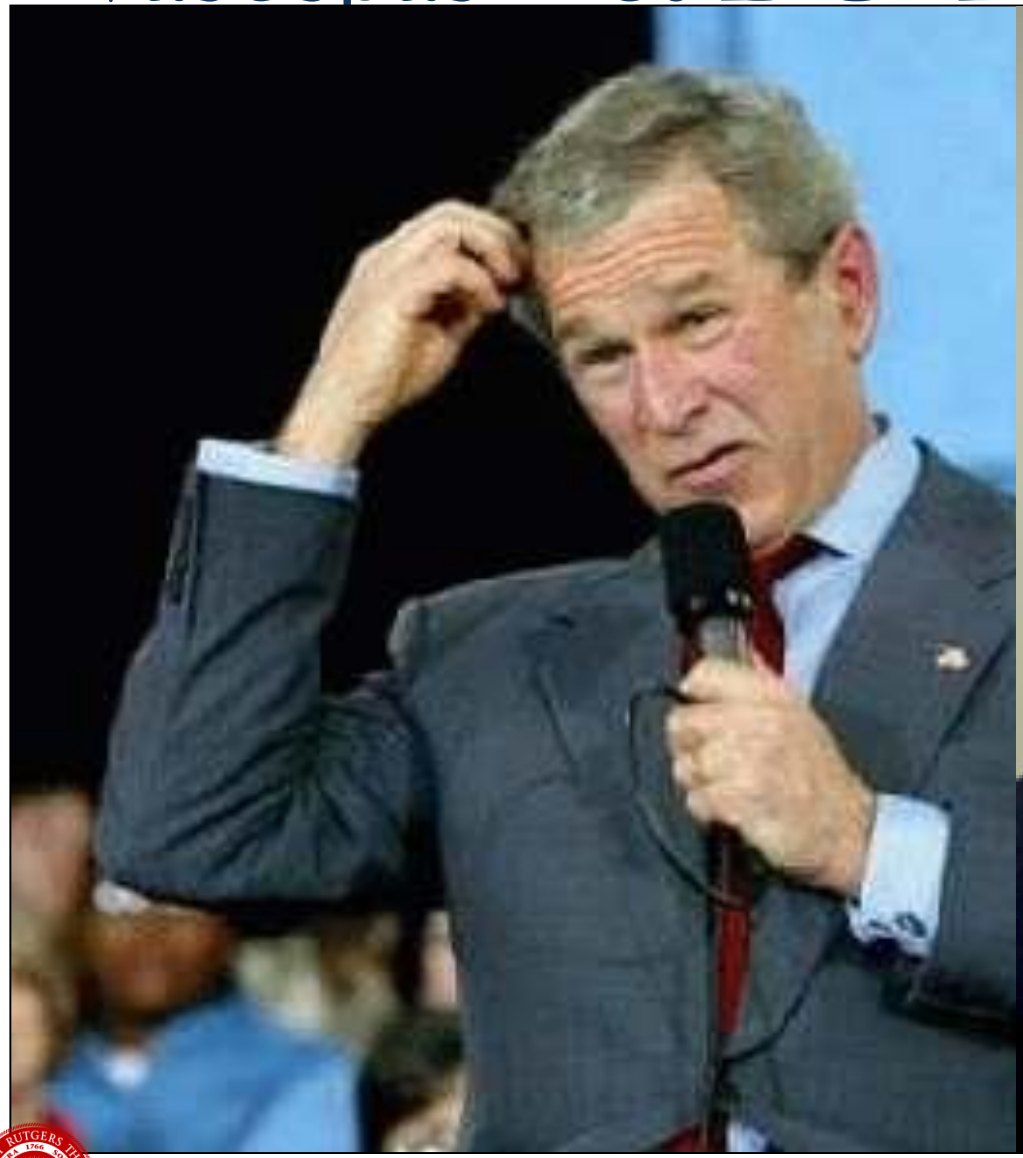
- Measures total intravascular CBF
- Disruption of the blood-brain barrier is a potential source of error.
- The use of relative values in CT perfusion can potentially be misleading in the setting of global vasospasm
- identification of ischemia caused by vertebrobasilar vaso





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Vasospasm & DCI Etiology





- The mechanisms leading to vasospasm of cerebral blood vessels and delayed cerebral ischemia following SAH are multifaceted and interdependent.

- It is unlikely that any one intervention is going to eliminate vasospasm.

- Immune dysregulation has long been implicated in the development of delayed cerebral ischemia (DCI) following aneurysmal subarachnoid hemorrhage (aSAH).

Cossu G, Messerer M, Oddo M, Daniel RT. To look beyond vasospasm in aneurysmal subarachnoid haemorrhage. *BioMed research international*. 2014;2014:628597

TRIPLE-H THERAPY (Hypertension, Hypervolemia, and Hemodilution

Normovolemic
Normodilutional
Hypertension

ar RH, Neurosurgery 12:658- 661, 1983 Egge A, Neurosurgery 49:593-605; discussion 605-606, 2001. TreggiariMM, J Neuro
Mayer SA, Fink ME, Beckford A, Paik MC, Zhang H, Wu YC, Klebanoff LM, Raps EC, Solomon RA: Effect of hypervolemic therapy on cerebral blood flow afte
rial. Stroke 31:383-391, 2000.

CALCIUM CHANNEL BLOCKERS

NIMODIPINE

- FDA approved in 1989 for vasospasm in good grade (HH 1–3) aSAH.
- MOA :Unknown
- 9 RCTs (Given orally in 5 trials and IV in 4 trials.)
- Largest RCT to date (554 patients),
- 60 mg of oral nimodipine Q4 hours for 21 days →Reduced strokes and poor clinical outcomes aswell as a reduction in 3-month mortality compared to patients given placebo.

- Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, Humphrey PR, Lang DA, Nelson R, Richards P,Sinar J, Bailey S, [illegible] A: Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British [illegible] MJ298:636-642, 1989.

CALCIUM CHANNEL BLOCKERS

NICARDIPINE

- 2 RCTs using nicardipine for the treatment and prevention of cerebral vasospasm

- Largest RCT on Nicardipine: 449 patients with IV nicardipine (0.15 mg/kg/hour, approximately 5–10 times the biologically equivalent dose of nimodipine approved for use in the United States) and 457 patients with placebo.

- Nicardipine- treated patients had significantly reduced vasospasm compared to patients who received placebo (32% vs. 46%, *P* 0.001), but clinical outcomes assessed using the Glasgow Outcome Scale (GOS) were similar between the groups at 3 months.

Haley EC Jr, Kassell NF, Torner JC: A randomized controlled trial of high-dose intravenous nicardipine in aneurysmal subarachnoid hemorrhage. A report of the Cooperative Aneurysm Study. J Neurosurg 78:537-547, 1993.

Capelle HH, Weidauer S, Weiss C, Munch E, Thome C, Luecke T, Schmiedek P, Kasuya H, Vajkoczy P: Effect of nicardip
vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: a prospective, randomized, double-blinc
2007.

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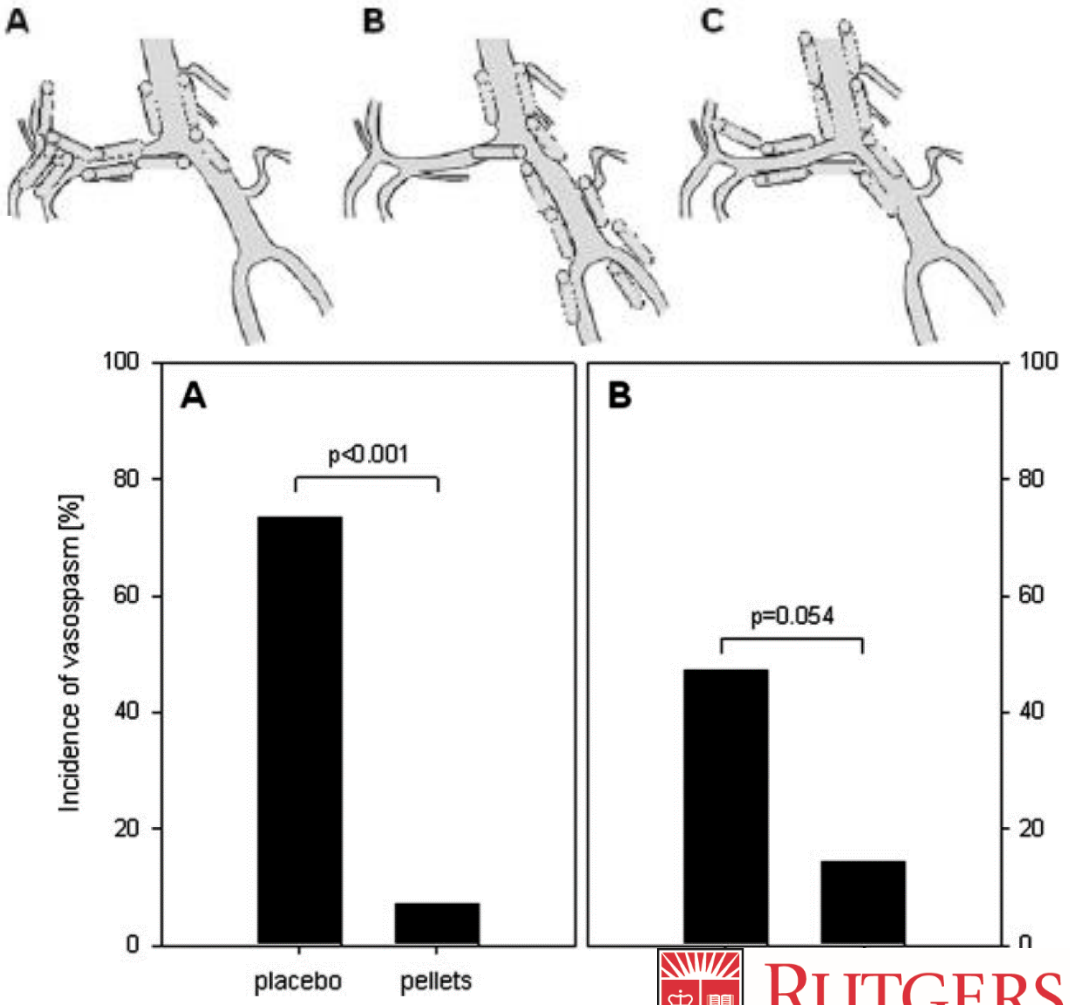
Effect of Nicardipine Prolonged-Release Implants on Cerebral Vasospasm and Clinical Outcome After Severe Aneurysmal Subarachnoid Hemorrhage

A Prospective, Randomized, Double-Blind Phase IIa Study

Martin Barth, MD; Hans-Holger Capelle, MD; Stephan Weidauer, MD; Christel Weiss, MD;

32 SAH patients undergoing clipping

NPRI pt demonstrated significantly reduced angiographic vasospasm incidence (*P* 0.05) and improved modified Rankin Scale scores at 1 year (*P* 0.0001) compared to 16 control patients.



Barth et al. Stroke. 2007;38:330-336.

CALCIUM CHANNEL BLOCKERS

FASUDIL

- Japanese experimental drug AT877: functions as a CCB via Rho-kinase signaling pathway inhibition, antagonizing the vasoconstrictive effects of endothelin by dilating cerebral arteries in animal vasospasm models.
- 2 RCTs
- A second RCT randomized 72 patients to either fasudil Vs continuous IV nimodipine for 14 days. Both drugs effectively reduced symptomatic vasospasm incidence, but fasduil demonstrated a non-significant, but greater, impact than nimodipine.
- NB: The nimodipine treated patients received approximately one-half the recommended treatment dosage. No significant differences were observed in the incidence of DCI, angiographic vasospasm, or clinical outcomes between the groups.

Zhao J, . Neurol Med Chir (Tokyo) 46:421-428, 2006.
Shibuya M, . J Neurosurg 76:571-577, 1992.

THROMBOLYTICS

- 2 RCTs and 1 meta-analysis using thrombolytic therapy for the prevention or treatment of cerebral vasospasm.

A 2004 meta-analysis studied 652 patients enrolled in nine trials(5 prospective and 3 retrospective studies).

- Significant absolute risk reductions for DCI (14.4%, *P* 0.001),
- Significant absolute risk reductions for poor GOS scores (9.5%, *P* 0.01),
- Significant absolute risk reductions of death (4.5%, *P* 0.05)
- No therapeutic difference was found between urokinase and tPA.

NB: Significant proportion of studies included in the meta-analysis were non-randomized.

MAGNESIUM

- Hypomagnesemia occurs in >50% of SAH patients
- 4 RCTs and 1 meta-analysis.
- In one RCT, a non-significant trends toward reduced mean MCA transcranial Doppler (TCD) velocities and improved GOS scores were observed in 20 patients treated with IV magnesium compared to placebo.
- No adverse events were noted following high dose magnesium administration in this study.
- Largest RCTs were the MASH trials

Veyna RS, J Neurosurg 96:510-514, 2002.

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Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage: A Randomized Controlled Trial

Walter M. van den Bergh

- MASH 1: RCT study of 283 SAH
- 64 mmol/L day (16 g/day) of Mg with goal to maintain Mg levels 1 – 2 mmol/L
- Treatment begun within 4 days of ictus
- Patients in the magnesium group:
  Non-significant reductions in DCI (34%,RR 0.66,95%CI 0.38 – 1.14) and poor clinical outcome at 3 months (23%, RR 0.77, 95% CI 0.54 –1.09) compared to placebo.
  Definitive benefit of magnesium therapy was not demonstrated in this study.

TABLE 2. Outcomes in the Trial According to Magnesium Treatment

	RR (95% CI)	NNT
Primary outcome		
DCI*	0.66 (0.38–1.14)‡	14 (35 NNTH to 6 NNTB)
Secondary outcomes		
New hypodensities on CT*	1.04 (0.79–1.37)	-
Poor outcome†	0.77 (0.54–1.09)	12 (37 NNTH to 5 NNTB)
Excellent outcome†	3.4 (1.3–8.9)	11 (7 NNTB to 43 NNTB)

Stroke. 2005;36:1011-1015

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Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial

Sanne M Dorhout Mees, Ale Algra, W Peter Vandertop, Fop van Kooten, Hans A J M Kuijsten, Jelis Boiten, Robert J van Oostenbrugge, Rustam Al-Shahi Salman, Pablo M Lavados, Gabriel J E Rinkel, Walter M van den Bergh, on behalf of the MASH-2 study group

Updated meta-analysis of seven randomised trials:

- 2047 patients shows that magnesium is not superior to placebo for reduction of poor outcome after aSAH (RR 0.96, 95% CI 0.84–1.10).

- Interpretation: Intravenous magnesium sulphate does not improve clinical outcome after aneurysmal subarachnoid hemorrhage, therefore routine administration of magnesium cannot be recommended.

Stroke. 2005;36:1011-1015

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Statins in the Management of Aneurysmal Subarachnoid Hemorrhage—Not (Yet) a Standard of Care

Andreas H. Kramer

Stroke. 2009;40:e80-e81; originally published online January 29, 2009;

STATINS

- Pleiotropic effects
- Reduce inflammation and cell proliferation
- Increase synthesis of nitric oxide by up regulation of eNOS
  - Improve vasoreactivity
- Prevent thrombogenesis

STATINS

- 5 RCTs and 1 meta-analysis

- Sillberg VA et al. published a meta-analysis of RCT of statin use in aneurysmal SAH

- Pooled results of 158 patients and found statistically significant reductions in vasospasm (RR 0.73, 95% CI 0.54–0.99), DCI (RR 0.38, 95% CI0.17– 0.83), and mortality (RR0.22, 95%CI0.06–0.82).

- The method used for diagnosing vasospasm differed between the three RCTs, which make them difficult to compare and possibly bias the conclusions of the meta-analysis.





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STATINS

- More recent RCTs have yielded less enthusiastic results using statins.

- In one trial by Chou et al., 39 patients were randomized to 80 mg of oral daily simvastatin or placebo.
  - Modest, but non-significant, reductions in angiographically confirmed vasospasm and DCI were observed for simvastatin-treated patients compared to placebo.

- Another RCT by Vergouwen, equally randomized 32 patients to receive simvastatin or placebo.
  - No difference in TCD-defined vasospasm or clinical outcome at 3- and 6-month follow-up was seen.

Chou SH, Stroke 39:2891-2893, 2008
Vergouwen, J Cereb Blood Flow Metab 29:1444-1453, 2009

NEUROCRITICAL CARE SOCIETY
IMPROVING OUTCOMES FOR PATIENTS WITH LIFE-THREATENING NEUROLOGICAL ILLNESSES

NCC Guidelines recommend:

Pt on statins prior to p/w aSAH should have their medication continued in the acute phase (Low Quality Evidence, Strong Recommendation).

Acute statin therapy in statin-naive patients may be considered for reducing DCI following aneurysmal SAH, pending the outcome of ongoing trials (Moderate Quality Evidence, Weak Recommendation)

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Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial

- **Favorable outcome (mRS 0–2):**
  - 271 pts in the simvastatin grp vs 289 in the placebo grp
  - The primary ordinal analysis of the mRS, gave a common odds ratio (OR) of 0.97, 95% CI 0.75–1.25;p=0.803

- **At 6 months:**

  - 37 (10%) deaths in the simvastatin group compared with 35 (9%) in the placebo group(p=0·592).

  - 70 (18%) serious adverse events were reported in the simvastatin group compared with 74 (18%) in the placebo group.

- **STASH did not detect any benefit in the use of simvastatin for long-term or short-term outcome in patients with aneurysmal subarachnoid hemorrhage.**

Kirkpatrick et al Lancet Neurology May 2014

TIRILAZAD

- Non-glucocorticoid aminosteroid that inhibits lipid peroxidation, functioning as a free radical scavenger.

- 4 RCTs (14, 23, 25, 26) and 1 meta-analysis (21)

- Results from the cooperative tirilazad trial in Europe, Australia, and New Zealand (Kassell NF et al.) were published in 1996. This trial enrolled 1015 patients randomized to receive high-dose tirilazad (6 mg/kg/day).

- Compared to patients randomized to receive placebo:
  - Significant reduction in overall mortality (*P* 0.01)
  - Significant improvement in 3-month clinical outcomes (*P* 0.01).
  - Non-statistically significant reduction in symptomatic vasospasm in high-dose tirilazad patients.
  - Male patients seemed to derive more benefit from the study drug than female patients.

Kassell NF, . J Neurosurg 84:221-228, 1996.
Haley EC Jr, J Neurosurg 86: 467-474, 1997.

TIRILAZAD

- Results were not replicated in the North American multicenter cooperative tirilazad trial (Haley EC Jr et al.)
  - 897 patients were randomized to receive low- (2 mg/kg/day) or high-dose (6 mg/kg/day) tirilazad or placebo.
    - No difference in symptomatic vasospasm incidence was observed between the three groups.
    - Incidence of DCI and neurologic decline was lower in the placebo arm
    - No clinical improvement at 3-month follow-up.

- 2 additional RCTs studied **female patients** only.
  - In 1999 (Lanzino G et al. A cooperative study in Europe, Australia, New Zealand,and South Africa) randomized 819 patients to receive tirilazad (n=405) or placebo (n =414) at 56 international centers.
  - In tirilazad- treated group :
    - Significant reduction in symptomatic vasospasm (33.7% vs 24.8%, P= 0.005).
    - Significant reduction in Incidence of DCI (8% Vs 13%, P 0.04)
    - No significant difference in the 3-month mortality rate

Lanzino G, J Neurosurg 90:1011-1017,1999.

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TIRILAZAD

- A 2009 meta-analysis by Jang et al. found:
  - –Significant reduction in symptomatic vasospasm for patients treated with tirilazad compared to placebo (OR0.80,95%CI 0.69–0.93)
  - –No significant reduction in unfavorable clinical outcome was observed.

- Tirilazad has been studied extensively in four large RCTs and has not been shown to consistently confer clinical benefit following aneurysmal SAH. It may, in fact, decrease good clinical outcomes in patients with admission WFNS grades I, II, or III.

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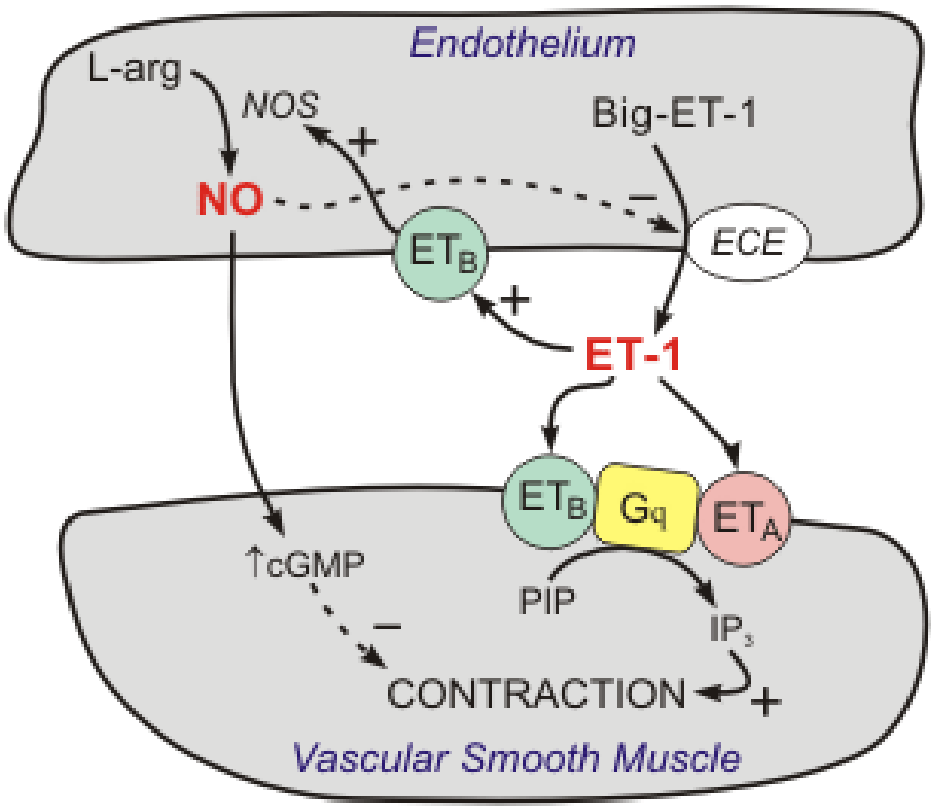
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ENDOTHELIN RECEPTOR ANTAGONISTS

- Endothelin is a potent, endogenous vasoconstrictor
  - Endothelin concentrations increased in CSF after SAH
  - Increased sensitivity of the cerebral arteri to endothelin after SAH.
  - Endothelin receptor antagonists reduce experimental vasospasm.

- Endothelin Receptor Antagonists inhibit the binding of endothelin 1,to its target receptors on vascular smooth muscle cells hence preventing its vasoconstrictive effe

- Clazosentan (AXV-034343) and TAK-044 are two examples of endothelin receptor antagonists.



http://www.cvpharmacology.com/vasodilator/ETblockers.htm

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ENDOTHELIN RECEPTOR ANTAGONISTS

The Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS- 1) trial

- Randomized 413 patients to either dose-escalated IV clazosentan (*n* 313) Vs placebo.
- Primary end point – moderate/severe angiographic VSP at PBD 7 to 11
- Three different doses of clazosentan (1, 5, or 15 mg/hour)

- Macdonald RL (CONSCIOUS-1) Stroke 39:3015-3021, 2008

ENDOTHELIN RECEPTOR ANTAGONISTS

CONSCIOUS- 1 trial

- Patients who received high-dose clazosentan (15 mg/hour) had:
  - Significantly reduced moderate and severe angiographic vasospasm (RR0.65, 95% CI 0.47– 0.78, *P* 0.0001) at day 9.

- All three dosages of clazosentan had:
  - Statistically significant reduction in moderate and severe angiographic vasospasm with the 15 mg/hour dosage having the greatest benefit.
  - Nonsignificant reductions in DCI were observed on post hoc analysis for patients who received clazosentan compared to placebo
  - No improvement in combined end point of morbidity/ mortality
  - **Increased pulmonary complications, hypotension, and anemia.**

- Macdonald RL (CONSCIOUS-1) Stroke 39:3015-3021, 2008

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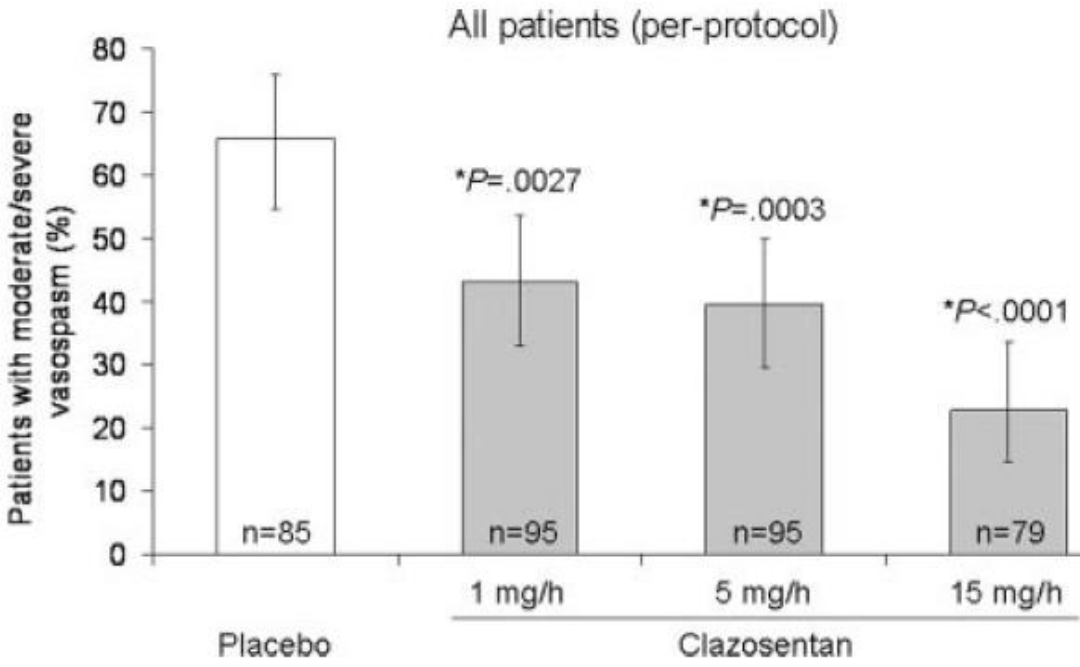
Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS-1)

Randomized, Double-Blind, Placebo-Controlled Phase 2 Dose-Finding Trial

R. Loch Macdonald, MD, PhD; Neal F. Kassell, MD; Stephan Mayer, MD; Daniel Ruefenacht, MD; Peter Schmiedek, MD; Stephan Weidauer, MD; Aline Frey, PharmD; Sebastien Roux, MD; Alberto Pasqualin, MD; on behalf of the CONSCIOUS-1 Investigators

Table 3. Adverse Events More Frequently Reported With Clazosentan Compared With Placebo

Characteristic	Placebo (n=96)	Clazosentan 1 mg/hour (n=107)	Clazosentan 5 mg/hour (n=110)	Clazosentan 15 mg/hour (n=96)
Hypotension	3 (3)	6 (6)	13 (12)	11 (12)
Anemia	16 (17)	27 (25)	32 (29)	19 (20)
Lung complications	26 (27)	47 (44)	48 (44)	37 (39)
Pulmonary edema	1 (1)	11 (10)	14 (13)	10 (10)
Acute respiratory distress syndrome	2 (2)	6 (6)	8 (7)	8 (8)
Pleural effusion	5 (5)	13 (12)	14 (13)	13 (14)
Pneumonia	14 (15)	21 (20)	25 (23)	13 (14)



PALLLIATIVE TREATMENT OF VASOSPASM

TRANSLUMINAL BALLOON ANGIOPLASTY

- The rate of major procedure-related complications was estimated to be 5% and the incidence of vessel rupture was 1.1%, according to the review by Hoh and Ogilvy.

- Some reported complications include thromboembolism, arterial dissection, reperfusion hemorrhage, branch occlusion, bleeding from untreated aneurysms, retroperitoneal hematoma, groin hematoma at the catheter site, and vessel rupture.

Suzuki S, Jahan R, Duckwiler GR, Frazee J, Martin N, Vinuela F. Contribution of endovascular therapy to the management of poor-grade aneurysmal subarachnoid hemorrhage: Clinical andangiographic outcomes. J Neurosurg 2006;105(5):664–670.

Hoh BL, Ogilvy CS: Endovascular treatment of cerebral vasospasm: transluminal balloon angioplasty, intra-arterial papaverine, and intra-arterial nicardipine. urg Clin N Am 16:501-516, 2005

berg-Lee M, Neurosurgery 2006;59(5 Suppl 3):S139–S147

JNS JOURNAL OF NEUROSURGERY
OFFICIAL JOURNALS OF THE AANS SINCE 1944

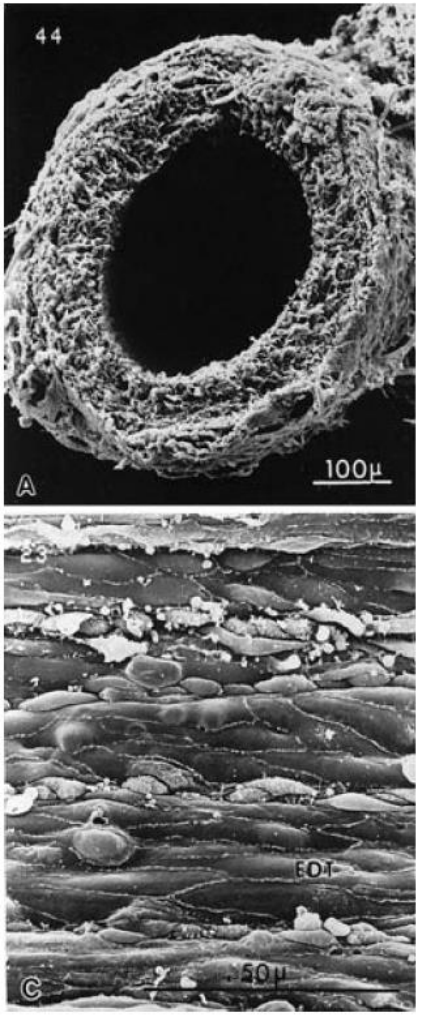
Journal of Neurosurgery
September 1995 / Vol. 83 / No. 3 / Pages 522-530

LABORATORY INVESTIGATIONS

Pharmacological and morphological effects of *in vitro* transluminal balloon angioplasty on normal and vasospastic canine basilar arteries

Patrick D. S. Chan, M.D., J. Max Findlay, M.D., Ph.D., Bozena Vollrath, Ph.D., David A. Cook, D.Phil., Michael Grace, Ph.D., Ming H. Chen, Ph.D., and Robert A. Ashforth, M.D.

- Ultra structural disruption of spastic vessels may be long lasting.
- Lower the incidence and severity of vasospasm
- Long-term effect balloon dilation on the vasculature are unclear.



disruption of the cellular or connective tissue elements.

Chan et al.J Neurosurg. 1995 Sep;8

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PALLLIATIVE TREATMENT OF VASOSPASM

TRANSLUMINAL BALLOON ANGIOPLASTY

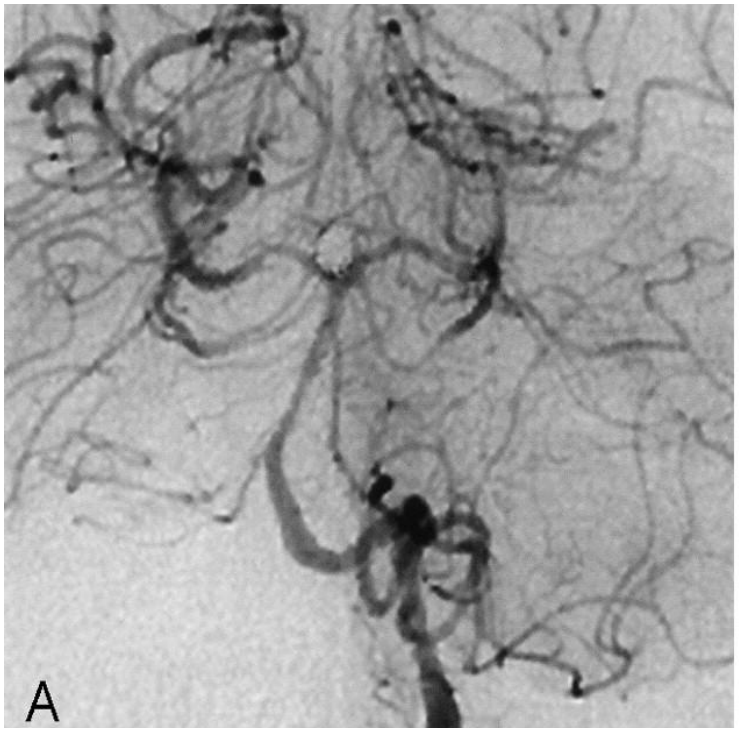
- **Efficacy:**
  - The effects of angioplasty were more sustained and thus required fewer treatments than papaverine . Despite these differences, some authors have advocated the integration of balloon angioplasty and intraarterial therapies as complementary rather than alternative techniques

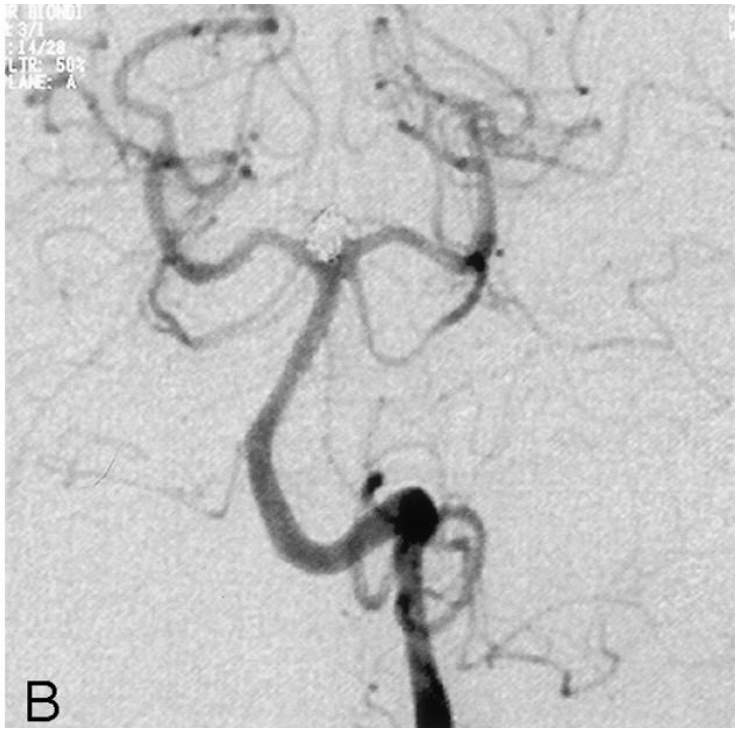
  - When angioplasty and intraarterial papaverine were compared, Elliott, et al. found balloon angioplasty to be superior to papaverine infusion in decreasing velocities measured by TCD (45 compared with 20% mean decrease, respectively).

  - Oskouian, et al., demonstrated a significant increase in CBF, from 33.3 to 41.7 ml/100 g/min, in 13 patients who received combined therapy. The TCD velocities decreased from 148.9 to 111.4 cm/second, with a mean increase in vessel diameter of 42.2%.

Elliott JP, et al. J Neurosurg 88: 277- 284, 1998
Oskouian RJ Jr, et al Neurosurgery 51:30-43, 2002
Eskridge JM, et al Neurosurgery 42: 510-517, 1998
Rosenwasser RH, et al Neuro surgery 44:975-980, 1999

PALLLIATIVE TREATMENT OF VASOSPASM
TRANSLUMINAL BALLOON ANGIOPLASTY







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Effect of Prophylactic Transluminal Balloon Angioplasty on Cerebral Vasospasm and Outcome in Patients With Fisher Grade III Subarachnoid Hemorrhage: Results of a Phase II Multicenter, Randomized, Clinical Trial

Marike Zwienenberg-Lee, Jonathan Hartman, Nancy Rudisill, Lori Kennedy Madden, Karen Smith, Joseph Eskridge, David Newell, Bon Verweij, M. Ross Bullock, Andrew Baker, William Coplin, Robert Mericle, Jian Dai, David Rocke and J. Paul Muizelaar

Stroke. 2008;39:1759-1765; originally published online April 17, 2008;

- Prophylactic TBA group experienced a non-significant reduction in DCI incidence (P=0.30) and a significant decrease in subsequent therapeutic angioplasty (P =0.03)

- Mid way in the trial the treatment protocol was revised to exclude angioplasty of the bilateral A1 and P1 segments where the majority of vessel perforations occurred.

- Although anecdotal reports suggest that TBA provides durable relief of vasospasm, no RCTs using therapeutic angioplasty alone have been published to date.

PALLLIATIVE TREATMENT OF VASOSPASM

INTRA-ARTERIAL DELIVERY OF VASODILATORS

- Papaverine
- Verapamil
- Nicardipine (+/- Magnesium)
- Milrinone
  - A case series of 8 patients diagnosed with aSAH who developed symptomatic cerebral vasospasm refractory to conventional medical therapy and received IA infusion of Milrinone at a rate of 0.25 mg/min, with a total dose of 10–15 mg.
    - All patients had a significant angiographic response. Improvement in stenosis from > 70% to < 50% post IA Milrinone infusion.
    - 3 pts developed recurrent vasospasm that improved after a second intra-arterial Milrinone infusion.
    - None of the patients developed neurologic or systemic complications attributed to the intervention.
    - At 3 months follow-up all patients were alive and had a mean mRS of 2 ± 1 and a Barthel index of 83 ± 10.

Badjatia N, AJNR Am J Neuroradiol 25:819-826, 2004
hah, et al Neurocrit Care (2009) 11:190–198
Milrinone (Romero et al Neurocrit Care (2009) 11:165–171)

INTRA-ARTERIAL DELIVERY OF VASODILATORS

- IA papaverine has an immediate effect on blood vessels, but reversal of clinical deficits is variable it has been largely abandoned because of its short lived effect and complications including increased intracranial pressure, apnea, worsening of vasospasm, neurological deterioration and seizures. This has led to growing use of intra-arterial nicardipine, verapamil, nimodipine, and milrinone as alternatives to papaverine

- IA nicardipine; Badjatia, et al, studied the use of IA nicardipine in 18 patients; and found an immediate angiographically confirmed dilation, and TCD ultrasonography studies revealed improvement in all vessels after intraarterial nicardipine treatment. Four days after treatment, the mean TCD velocities had improved significantly, from 268.9cm/second to 197.6 ± 74.1 cm/second. Clinical neurological improvement was reported in 42% of posttreatment neurological examinations.
- Main adverse effect was an increase in ICP in six (33%) of 18 patients that resolved after the ventriculostomy was opened.

Brisman JL, Neurol Res 2006;28(7):769–776. Mueller-Kronast N, Curr Treat Options Neurol 2007;9(2):146–157.

Jestaedt L, Neurosurgery 2008;62(3):610–617.

Cross DT III, AJNR Am J Neuroradiol 1998;19(7):1319–1323. Milburn JM, AJNR Am J Neuroradiol 1997;18(6):1081– 1085.

Sayama CM, Neurosurg Focus 2006;21(3):E12

Badjatia N, Topcuoglu MA, Pryor JC, Rabinov JD, Ogilvy CS, Carter BS, et al: Preliminary experience with intra-arterial nicardipine as a treatment for cerebral vasospasm. AJNR Am J Neuroradiol 25:819-826, 2004





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INTRATHECAL NICARDIPINE

- One retrospective analysis(Emory)
  - 42 patients → IT (preservative free) Nicardipine 4 mg Q 8–12 h.
  - An equivalent volume of CSF was withdrawn prior to administration. Ventricular drain was then clamped for 30 min and reopened.
  - Reduction of the mean cerebral blood flow velocity of 26.3 cm/s in the middle cerebral artery and 7.4 cm/s in the anterior cerebral artery.
  - Reduction was maintained over 24 h with continued administration.

1. Goodson, et al. Neurocrit Care (2008) 8:247–252
Ehtisham A et al. South Med J. 2009 Feb;102(2):150-3
Webb A & Samuels O et al . Neurocrit Care. 2010 Apr;12(2):159-6

Performance of Bedside Transpulmonary Thermodilution Monitoring for Goal-Directed Hemodynamic Management After Subarachnoid Hemorrhage

Tatsushi Mutoh, MD, DVM, PhD; Ken Kazumata, MD;
Tatsuya Ishikawa, MD; Shunsuke Terasaka, MD

Patients receiving early goal-directed management by transpulmonary thermodilution experienced:
Reduced frequencies of vasospasm and
Reduced frequencies of cardiopulmonary Cx compared with those managed with standard therapy ($P<0.05$), whereas their functional outcomes at 3 months were not different ($P=0.06$).

Table. Clinical Characteristics of Patients With SAH

	PiCCO-Guided Management	Conventional Management
No. of patients	50	50
Sex, male/female	17/33	20/30
Age, years	64±10	63±11
WFNS grade		
I	12	15
II	14	11
III	2	4
IV	17	16
V	5	4
Fisher grade		
3	42	40
4	8	10
Aneurysm location		
ACoA/ACA	16	17
MCA	18	18
ICA	14	13
Other	2	2
mRS at 3 months		
0	3	2
1	8	6
2	8	7
3	9	7
4	13	18
5	9	10

WFNS indicates World Federation of Neurological Societies; ACoA, anterior communicating artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; ICA, internal carotid artery; mRS, modified Rankin Scale.

Stroke. 2009;40:2368-2374

Stroke

American Heart Association | American Stroke Association

Multicenter Prospective Cohort Study on Volume Management After Subarachnoid Hemorrhage Hemodynamic Changes According to Severity of Subarachnoid Hemorrhage and Cerebral Vasospasm - SAH PiCCO Study Group

- Multicenter prospective cohort study of hemodynamic variables from days 1 to 14 was performed using a transpulmonary thermodilution system (PiCCO Plus). advanced hemodynamic hemodynamic monitoring.

- Patients with poor grade SAH developed heart failure-like afterload mismatch at an early stage, and those with DCI had decreased global end-diastolic volume index (hypovolemia) in the early stage of SAH.

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Effect of triple-h prophylaxis on global end-diastolic volume and clinical outcomes in patients with aSAH.

SAH PiCCO Study Group.

- Prospective multicenter study 9 hospitals in Japan.
- Decision to administer prophylactic triple-H therapy and the management protocols were left to the physician in charge (physician-directed therapy). Primary endpoints were the changes in the hemodynamic variables as measured using PICCO catheter.

RESULTS

- Of 178 patients, 62 (34.8 %) received prophylactic triple-H therapy and 116 (65.2 %) did not.
- Despite greater amount of fluid ($p < 0.001$) and a higher mean arterial pressure ($p = 0.005$) in the triple-H group, no significant difference was observed between the groups in GEDI ($p = 0.81$) or cardiac output ($p = 0.62$).





Summary

Detection

- CT angiography/ perfusion is a real advancement in detection
  - Prospective studies investigating optimal timing, sequence acquisition needed

Prevention

- Several preventative therapies under active investigation
  - Doubt any single one will provide significant relief
  - Combinations may hold more promise

Palliation

- Getting back to "basics" of optimizing cardiac performance??
- Intrathecal drug delivery an effective Rx for "distal" spasm
  - PK and PD studies
  - afety profile - risk for ventriculitis
  - Which cocktail: nicardipine only, nicardipine and other drugs?





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Prudential







PiCCO vs PAC Management

PiCCO-GuidedManagement

- Brachial artery ≤ PBD 4 measurements at least twice/day until PBD14.
- Intravascular volume expansion with 6% hydroxylethyl starch after PBD 4 if CI <3.0 L/min/m2 due to hypovolemia <GEDI 680 mL/m2.
- If TCD vasospasm and HES ineffective in raising GEDI and low CI persisted for at least 12 hours, supplemental 25% albumin solution (50 to 100 mL/d)
- If the low CI despite hypervolemia and maximum fluid therapy for at least 12 hours, then dobutamine
- When DIND diagnosed, the CI raised (3.5 L/min/m2) and managed with with dobutamine (3 to 20 g/kg/min)

Conventional Management

- Patients maintained under euvolemia with CVP of 5 to 8 mm Hg by supplemental crystalloids (500 to 1500 mL/d)
- If DIND was present, PAC placed – goal PCWP of 12 to 16 mm Hg or, if only CVP is available, levels of 8 to 12 mm Hg with hemodynamic augmentation (cardiac index 3.5 L/min/m2) initially with HES followed by supplemental 25% albumin and, finally, enhancement of cardiac contractility with dobutamine.
- PA Line monitoring was initiated only when DIND was suspected, measured at least twice daily, and placement never exceeded 7 days.
- Daily fluid balance aimed to keep at 500 mL positive by adjusting intravenous fluid administration.





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PiCCO vs PAC

- CI measurement (n=16)
  - TPCI and PCCI comparable to PAC CI measurement
- Fluid responsiveness (n=16)
  - GEDI better showed better sens/spec for predicting fluid responsiveness (>10% SVI)
- Assessment of Pre load (n=16)
  - PiCCO better correlation with delta SVI
- Maintenance of euvoluemia (n=100)
  - PiCCO better than conventional
- Less Cardiac complications (n=100)

