

# Present and Future Medical Treatment of Cerebral Vasospasm



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# Subarachnoid Hemorrhage

## Etiology



- SAH may be spontaneous or traumatic
- Spontaneous SAH caused by:
  - Cerebral aneurysms (~72%)
  - AV malformation (~10%)
- Uncommon causes - neoplasms, dural AVM, venous angiomas, infectious aneurysms

# Subarachnoid Hemorrhage

## Epidemiology

- 5-7% of all stroke cases
  - Incidence 10/100,000/yr
- 40% mortality
- 50% of survivors experience severe neurological deficits
- 1-2% of population have unruptured aneurysms
- Women > men
- Incidence increases linearly with age
  - Mean age of onset 51 years
- 10-15% of patients presenting with SAH have multiple aneurysms

# Subarachnoid Hemorrhage

## Influencers of Outcome

### Patient Factors

Severity of initial hemorrhage  
Age  
Gender  
Time to treatment  
Comorbidities (HTN, CHF, renal disease, afib, CAD)  
Aneurysm size & location

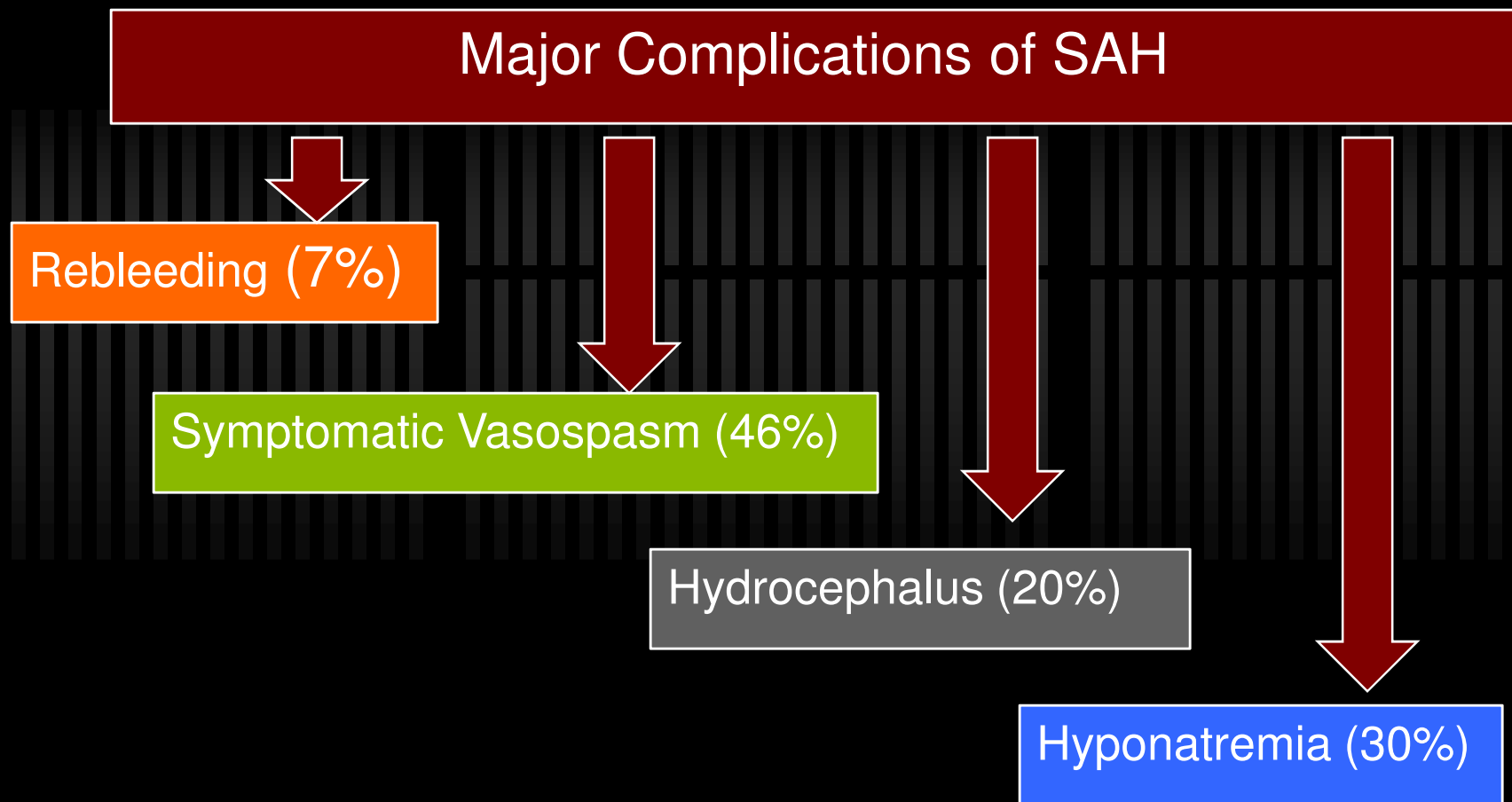
### Institutional Factors

Availability of endovascular services  
Volume of SAH pts treated  
Type of facility that 1st evaluates pt

### Associated Pathophysiological Processes Linked to Acute SAH

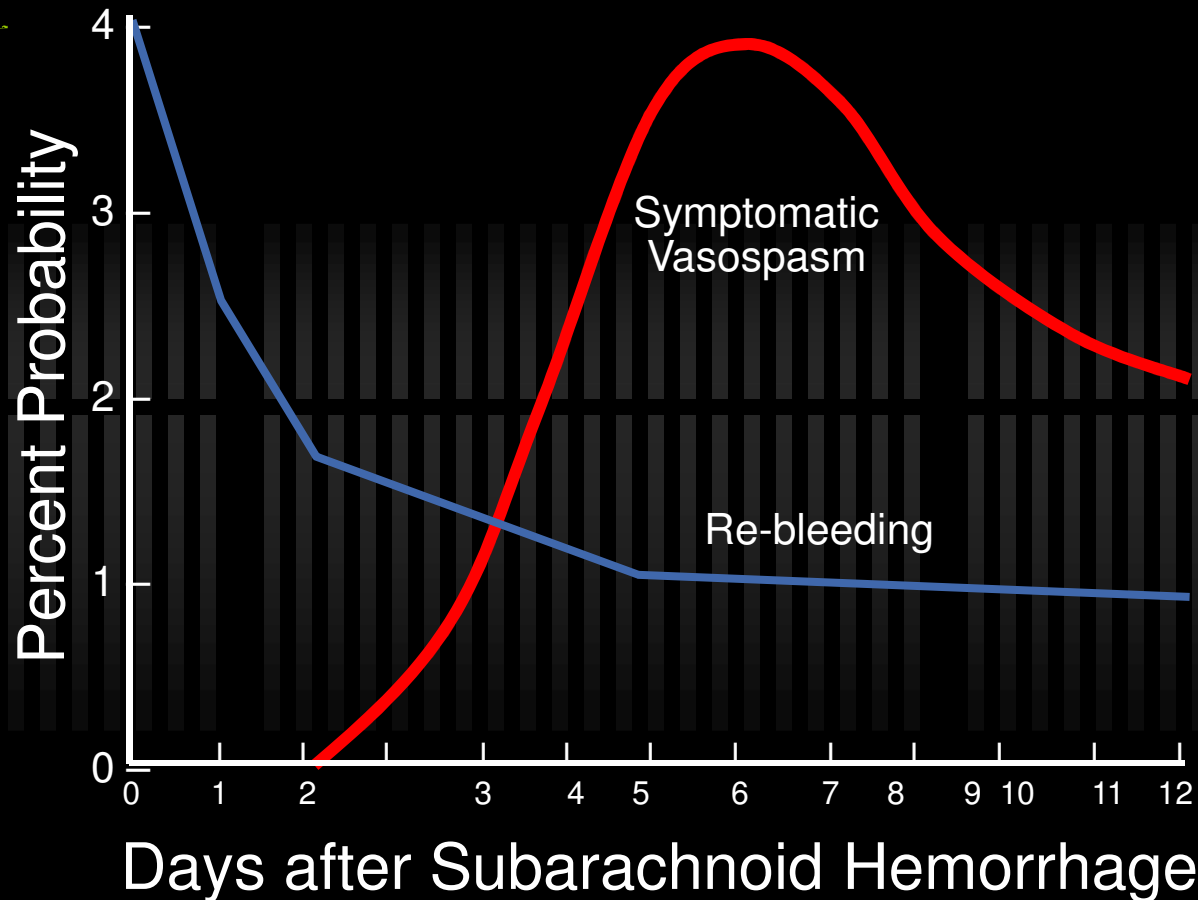
↑ ICP & ↓ CPP  
↓ availability of NO  
Acute vasoconstriction  
Microvascular platelet aggregation  
Activation of microvascular collagenases  
Loss of microvascular collagen  
↑ microvascular permeability

# Subarachnoid Hemorrhage Complications



# Complications Following SAH

## Rebleeding and Vasospasm



The daily percentage probability for the development of symptomatic vasospasm or re-bleeding after subarachnoid hemorrhage.

# Cerebral Vasospasm

## Overview

- Incidence
  - 70% of patients with radiographic vasospasm
  - 46% of patients with symptomatic vasospasm
- Onset
  - Symptomatic vasospasm typically appears 3-4 days after aneurysm rupture
  - Peak incidence 7 to 10 days after rupture
  - Risk beyond 3 weeks is low
- Main consequence is delayed neurologic ischemic deficits (DIND)
- DIND effect on outcome
  - 50% progress to cerebral infarctions
  - 34% have permanent deficits
  - 30% of patients die
- Various methods of detection including imaging and clinical examination

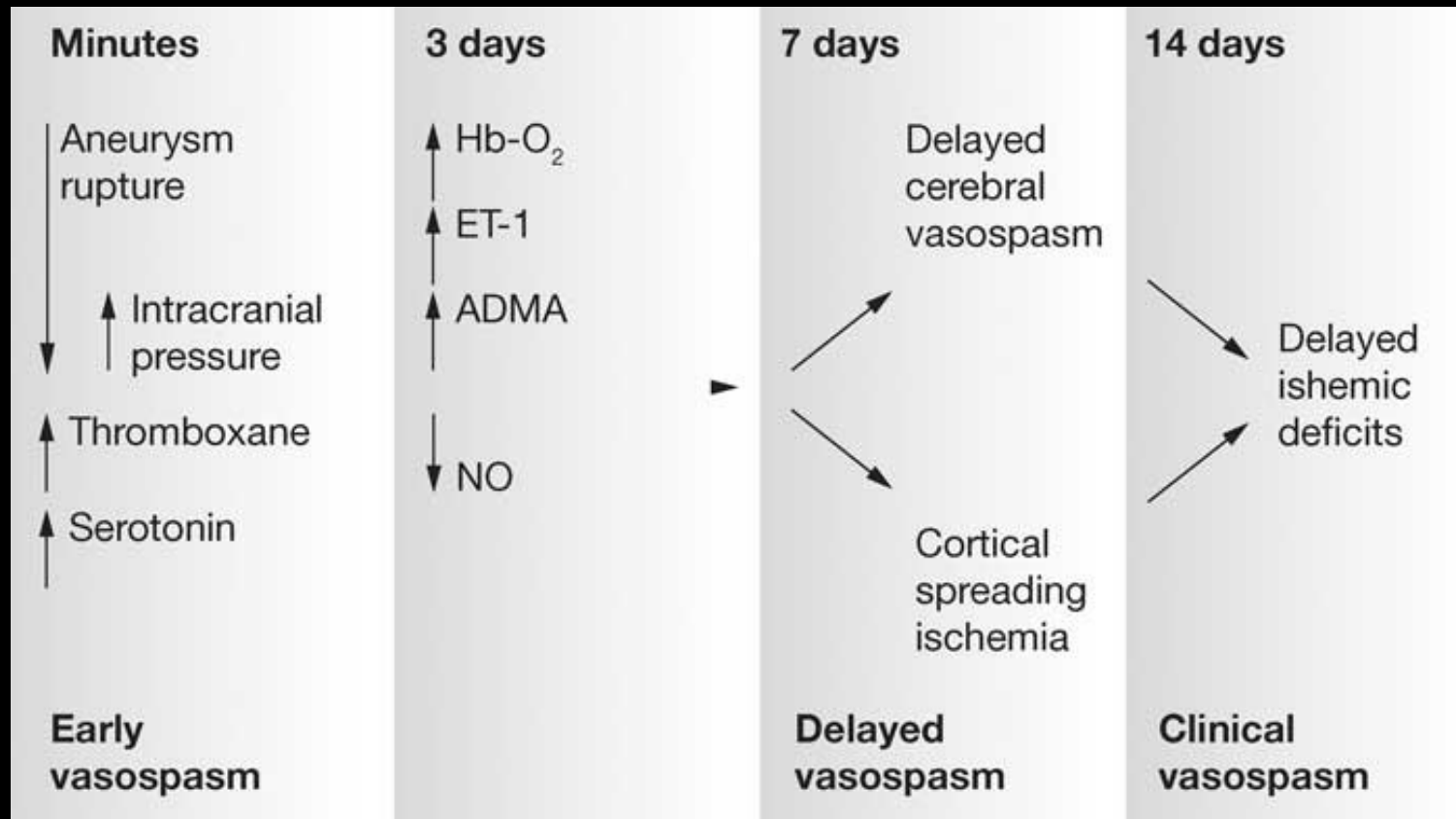
# Cerebral Vasospasm

## Risk Factors

- Age younger than 35 and older than 65
- History of hypertension & prophylactic use of induced hypertension
- Cigarette smoking
- Cocaine abuse
- Fisher grade (large blood burden and presence in lateral ventricle)
- Worse neurological grade
- Size and location of aneurysm
- Increased ICP

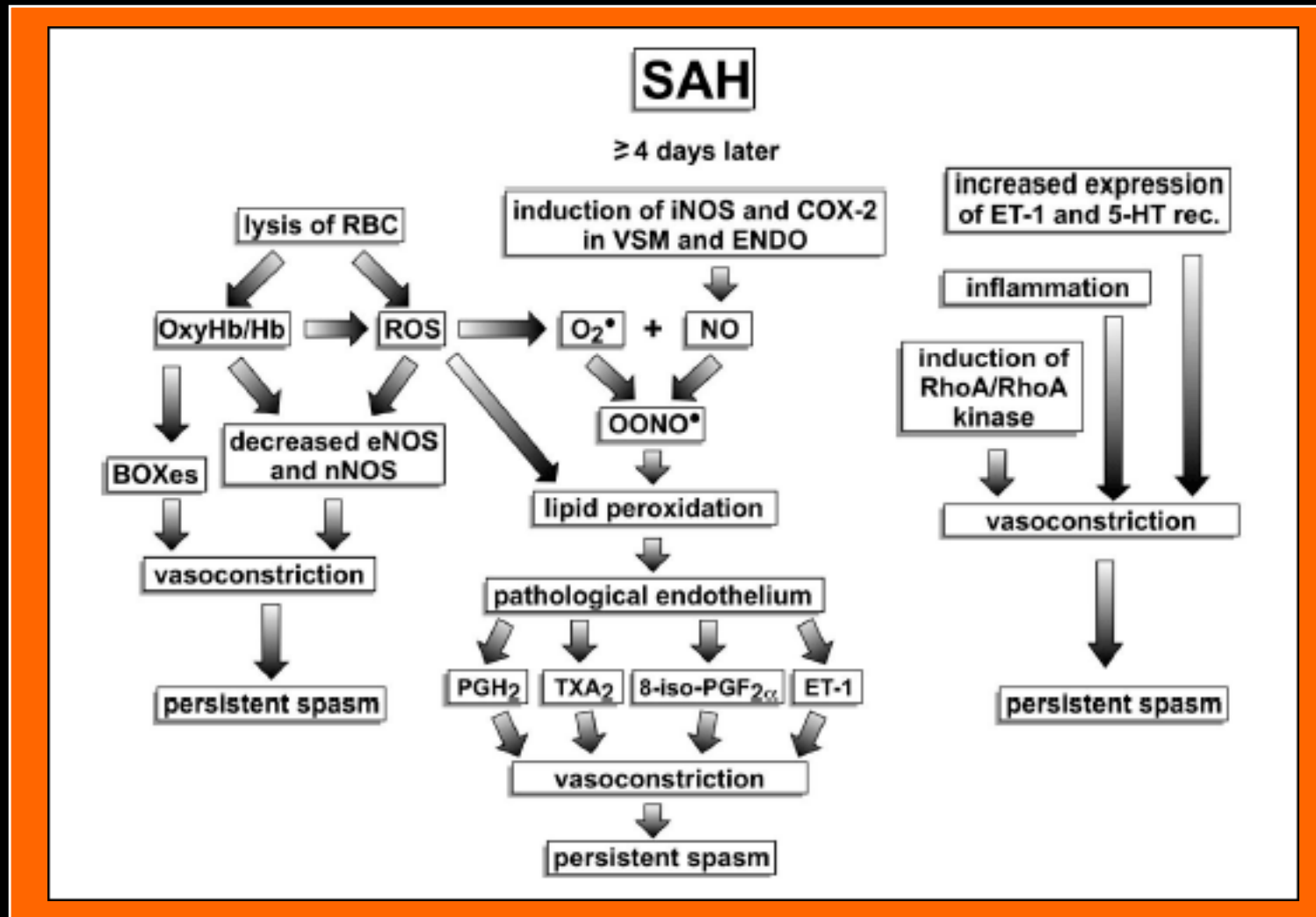
Harrod CG, et al. Neurosurgery 2005;56:633-654.  
Janjua N et al. Curr Opin Crit Care 2003;9:113-119.  
Macdonald RL, et al. J Neurosurg 2003;99:644-52.

# Time course of the pathophysiology of delayed cerebral vasospasm and clinical vasospasm



# Cerebral Vasospasm

## Mechanism of Delayed Vasospasm



# Cerebral Vasospasm

## Present & Future Management



Cerebral Vasospasm

Prophylaxis	
Present	Remove clot Nimodipine Normothermia Euvolemia
Future	Statins Magnesium Thrombolytics Endothelin antagonist EPO

Treatment	
Present	Triple-H therapy Endovascular intervention Cardiac output augmentation
Future	Intraventricular nicardipine Albumin NO donors

# Present and Future Prophylactic Interventions



Evidence Based Discussion

## AHA/ASA Guideline

### Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage

A Statement for Healthcare Professionals From a Special Writing Group  
of the Stroke Council, American Heart Association

Joshua B. Bederson, MD, Chair; E. Sander Connolly, Jr, MD, FAHA, Vice-Chair; H. Hunt Batjer, MD;  
Ralph G. Dacey, MD, FAHA; Jacques E. Dion, MD, FRCPC; Michael N. Diringer, MD, FAHA;  
John E. Duldner, Jr, MD, MS; Robert E. Harbaugh, MD, FAHA;  
Aman B. Patel, MD; Robert H. Rosenwasser, MD, FAHA

Goals of Cerebral Vasospasm Management is to ↓ the threat of ischemic neuronal damage by:

- Controlling ICP
- ↓ metabolic rate of O<sub>2</sub> use
- Improving CBF

Published in Stroke online January 22, 2009

# Calcium Channel Blocker Rationale

- Exact mechanism is unclear (L-type calcium channel antagonists)
- Postulated mechanisms
  - € ↓ intracellular calcium levels
  - € Selective relaxation of cerebral arterial smooth muscle
  - € Opening up of small vessel collaterals
  - € Increases fibrinolytic activity (↑ tpa antigen; ↓ PAI-1)
- Agents Studied = nimodipine, nicardipine, diltiazem
- Diltiazem had no impact on vasospasm incidence or outcome
- Nicardipine showed evidence that high dose decreased vasospasm by 30% but did not impact outcome
  - It was postulated that hypotension affected outcome
- Multiple clinical trials have made nimodipine a mainstay therapy

Vergouwen MDI, et al. J Cereb Blood Flow Metab 2007;27:1293-308

Feogom VL, et al. Neurology 1998;50:876-83

Haley EC, Jr, et al. J Neurosurg 1993;78:537-47

# Nimodipine

## Literature Review

### ■ Cochrane analysis

- Conclusion: Oral nimodipine 60mg PO every 4 hours within 96hrs for 21 days is recommended for the prophylaxis of vasospasm secondary to aSAH
- Nimodipine improves neurologic outcomes but does not prevent cerebral vasospasm
- Hypotension is the most common side effect (4.4% of patients)

Outcome	RR	95% CI
Poor outcome (death or dependence)	0.70	(0.55 – 0.81)
Case fatality	0.80	(0.63 – 1.03)
Clinical signs of ischemia	0.64	(0.49 – 0.83)
Rebleeding during clinical course	0.75	(0.53 – 1.04)

NNT to prevent 1 poor outcome = 20

# Calcium Channel Blocker SAH Guideline Recommendation

- Oral nimodipine is indicated to reduce poor outcome related to aneurysmal SAH (**Class I, Level of Evidence A**). The value of other calcium antagonists, when administered orally or intravenously, remains uncertain

# Magnesium

## Rationale

- 50% of SAH patients have hypomagnesemia & is associated with secondary cerebral ischemia and poor outcome
- May be involved in multiple pathophysiological pathways involved in genesis of cerebral vasospasm
  - Causes smooth muscle relaxation and vasodilation
  - Antiplatelet effects
  - Noncompetitive NMDA antagonist
    - ✓ Reverses cerebral vasospasm & ↓ infarct volume after experimental SAH
  - Inhibits glutamate by enhancing the effect of adenosine on Mg-dependent presynaptic adenosine 1 receptors
  - Inhibits an enzyme that produces the superoxide radical

Liu-DeRyke X et al. *Pharmacotherapy* 2006; 26(2):182-203.  
McKee JA et al. *Crit Care Med* 2005; 33:661-666.

# Magnesium - Literature Review

Study	Mg Regimen	Outcome
Veyna et al J Neurosurg 2002 (n=40)	6g bolus, 2g/hr to maintain Mg of 4-5.5mg/dL x 20d started within 72 hrs vs placebo	No serious AE; trend towards better outcome
van den Bergh et al Stroke 2005 (n=283)	16 gm/d to maintain Mg of 2.4-4.8mg/dL x 14-18d started within 96 hrs vs placebo	Reduced risk of DIND by 34% RR for poor outcome: 0.77 Termination: ↓BP (n=1), ↓HR & A fib (n=1), ↑Mg (n=1)
Schmid-Lisaesser et al Neurosurgery 2006 (n=104)	10mg/kg bolus, 30 mg/kg/d Mg (7 days IV then 7 days PO) vs. nimodipine started within 96 hrs	No serious side effects No difference in outcome
Muroi et al Surg Neurol 2008 (n=58)	1.9g bolus, 7.7g/d to maintain Mg up to 4.8mg/dL x 12 days started within 72hrs vs. placebo	Trend of improving TCD-detected vasospasm & better outcome @ 3mos
Wong et al. J Neurosurg Anesthesiol 2006 (n=60)	5 gm over 30min then 1gm/hr x 14 days vs. placebo	Symptomatic vasospasm (43% vs 23%; p=0.06); duration of vasospasm shorter in Mg group; no difference in outcome
Stippler et al. J Neurosurg 2006 (n=76)	12 mg/day x 12 days started within 48 hrs compared to historical controls	Significant symptomatic vasospasm (18% vs 42%) Trend towards improved outcome

# Statins

## Rationale

- Improves endothelial dysfunction
- Anti-inflammatory properties
- Improves autoregulation
- Improves CBF
- ↓ cerebral vasospasm

### Proposed mechanisms of beneficial effects

- Inhibits [NAD(P)H] oxidase and superoxide production
- Up-regulation and activation eNOS and increased NO via inhibition of geranylgeranylation of RhoA and Rac1 guanosine triphosphatases

# Satins - Literature Review

Study	Interventions	Design	Outcome
Lynch JR et al (n=39)	Simvastatin 80mg daily vs. placebo	Start within 48h for 14 d	Significantly lower in MCA velocity; Significant reduction in clinical vasospasm 26% vs 60%); Serum biomarkers (vWF & S100 $\beta$ ) of brain injury were significantly ↓ 3-10 days after SAH
Tseng MY et al 2005 (n=80)	Pravastatin 40mg daily vs. placebo	Start within 72 h, for up to 14 d	Significant reduction in vasospasm (42.5% vs 62.5%) & severe vasospasm (17.5% vs 30%); neurologic deficits (5% vs 30%) and mortality (5% vs 20%) were also decreased significantly
Tseng MY et al 2007 (n=80) FU ANALYSIS			Vasospasm related mortality & use of rescue therapy significantly reduced; pravastatin decreased unfavorable outcomes at discharge and at 6 months
Chou SHY et al. (N=39)	Simvastatin 80mg/day vs. placebo	Continued to Discharge or max 21 days	No mortality difference (3 pts in placebo vs. 0) TCD VSP higher in statin group (68% vs 50%; p.0.05); no difference infarct (11% vs 25%)

Lynch JR et al. Stroke. 2005; 36: 2024-26.

Tseng MY et al. Stroke. 2005; 36: 1627-1632.

Chou SHY et al. Stroke 2008;39:2891-2893

Tseng MY et al. Stroke. 2007; 38:1545-50.

# Satins

## Meta-Analysis

- Included 3 trials

- Incidence of vasospasm RR=0.22 [95%CI 0.54-0.99]

“The assertion in this meta-analysis is too strong”  
AH Kramer

- Mortality RR=0.22 [95% CI 0.06-0.82]

“Medicine has a poor track record of premature adoption of therapies based on single or small randomized controlled trials which have turned out to be ‘wrong’”  
Cook and Hessel

Sillberg VAH, et al. Stroke 2008;39:2622-2626  
Kramer AH. Stroke published Jan 28, 2009 [Epub]  
Cook AM, Hessel EA. Stroke published Jan 28, 2009 [Epub]

# Statins

## Institutional Experience

Study	Intervention	Outcome
McGirt MJ, et al. J Neurosurg 2006;105:671-674	Assessed statin use for $\geq$ 1mo PTA in 115 consecutive patients	Statin therapy regardless of age, clot load, clinical status or aneurysm location $\downarrow$ odds of developing vasospasm 11-fold
Parra A, et al. Neurosurgery 2005;56:476-84.	20 statin users 40 nonstatin users	Statin users had significantly improved outcome @ 14d; lower incidence DIND & infarctions
Kramer AH, et al. Neurosurgery 2008;62;422-430	Per institutional protocol initiated Simvastatin 80mg/d x 14d 71 statin vs 79 untreated	Statin use was <u>not</u> associated with $\downarrow$ in vasospasm, delayed infarction or poor outcome
Kerz T, et al. Neurol Res 2008; 30:893-897	Started Simvastatin 20mgx3d then 40mg/d x 10 days + Mag oxide 80 mmol/d Statin only 21 pts vs 28 pts S+mg vs 51 pts untreated	Trend towards lower mortality in patients treated with S or S+Mg; Higher incidence of DIND in statin group(24%) compared to S+Mg (18%) or untreated (16%) $p>0.05$

# Statins

## *Increase Risk of Vasospasm?*

Retrospective evaluation of 514 SAH pts; 36 pts were receiving statins upon admission (19 pts had statin D/C upon admission)  
Vasospasm documented in 62% of patients; 29% symptomatic

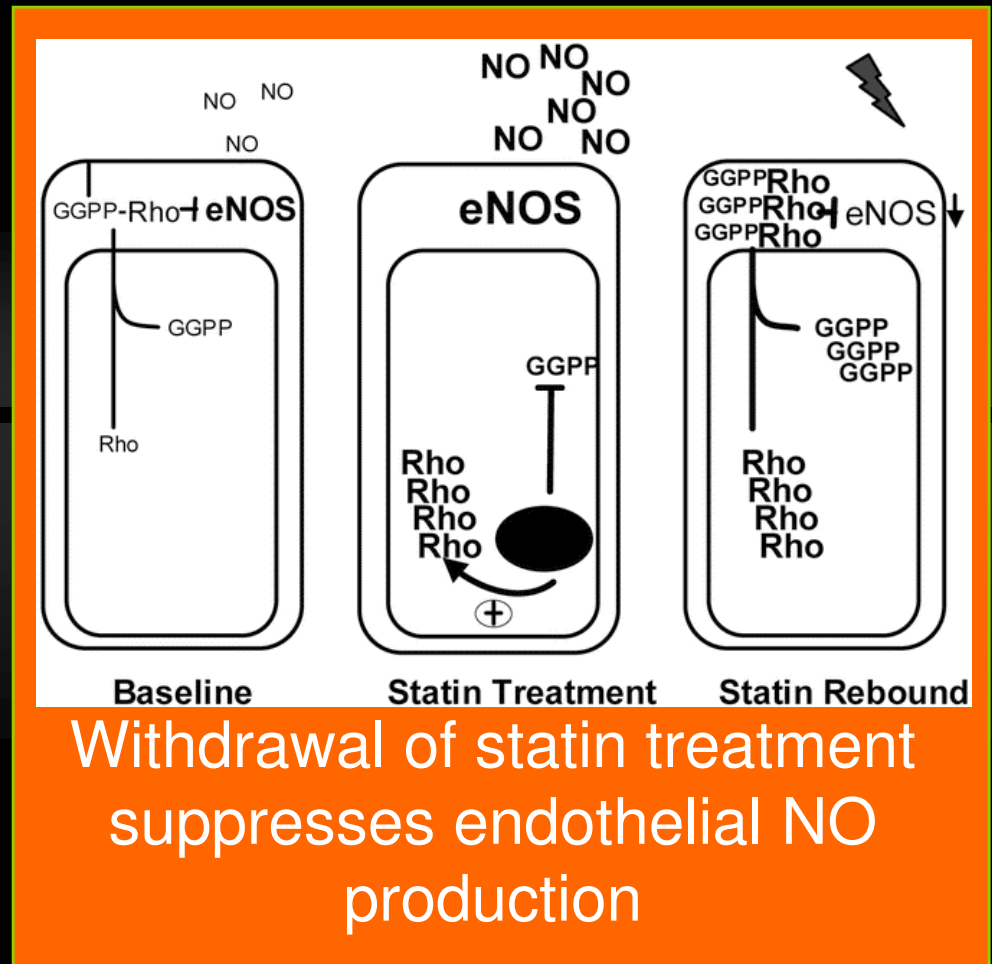
*Table 4 Multivariate analysis (logistic regression)*

Variables in the model	All vasospasm		Symptomatic vasospasm	
	OR (CI)	<i>p</i> Value	OR (CI)	<i>p</i> Value
Age (decades)	0.70 (0.61–0.80)	<0.0001	0.87 (0.75–1.02)	0.087
Hunt-Hess grade 4 or 5	1.44 (1.20–1.74)	0.0001	1.58 (1.30–1.92)	<0.0001
Fisher group 3	2.00 (1.31–3.05)	0.0014	2.06 (1.27–3.33)	0.003
SSRI	2.01 (0.91–4.45)	0.08	1.42 (1.06–4.33)	0.033
Statin	2.75 (1.16–6.50)	0.021	1.43 (0.66–3.08)	0.36

Statin users were found to be at higher risk of vasospasm but not symptomatic vasospasm

# Statin Withdrawal

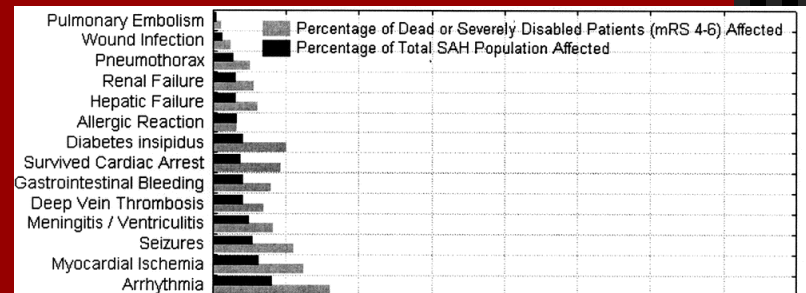
- **Baseline**
  - Rho in active & inactive form
- **During Statin Treatment**
  - Formation of GGPP is blocked and RHO is only present in inactive form
  - Upregulation of eNOS  $\Rightarrow \uparrow$ NO
  - Via negative feedback upregulation  $\Rightarrow \uparrow$  Rho GPTase gene transcription  $\Rightarrow \uparrow$  inactive Rho
- **Statin Withdrawal**
  - GGPP becomes available  $\Rightarrow \uparrow$  activated Rho  $\Rightarrow$  suppression of eNOS expression and  $\downarrow$ NO



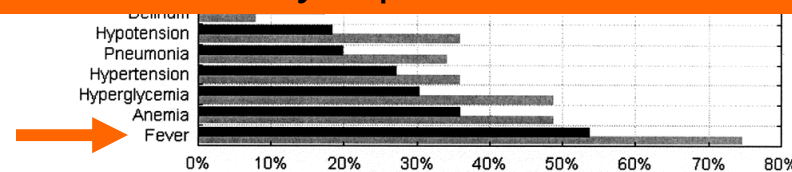
# Normothermia (Hypothermia?)

## Rationale

- Experimental models of ischemia suggest hypothermia is effective in reducing neuronal damage after SAH
- Intraoperative hypothermia (35-38 °C) during aneurysm surgery has been reported with varying results (no benefit to CBF improvement)
- Small studies suggest mild hypothermia (32-34 °C) may be helpful in refractory vasospasm



Fever was most frequent medical complication after SAH & is significantly associated with mortality & poor functional outcome



Wartenberg KE, et al. Crit Care Med 2006;34:617-623

Naval NS, et al. Crit Care Med 2006;34:511-524

# Endothelin and SAH

Endothelial A receptors mediate vasoconstriction in arterial smooth muscle [Vajkoczy P, et al. . J Neurosurg 2005;103:9-17](#)

Patients in whom angiography revealed diffuse moderate-to-severe vasospasm had significantly higher ET levels than other patients within 24 hours

[Juvela A. J Neurosurg 2000;92:390-400](#)

ET-1 concentration in CSF showed a significant increase over time with highest values on day 5 post ictus

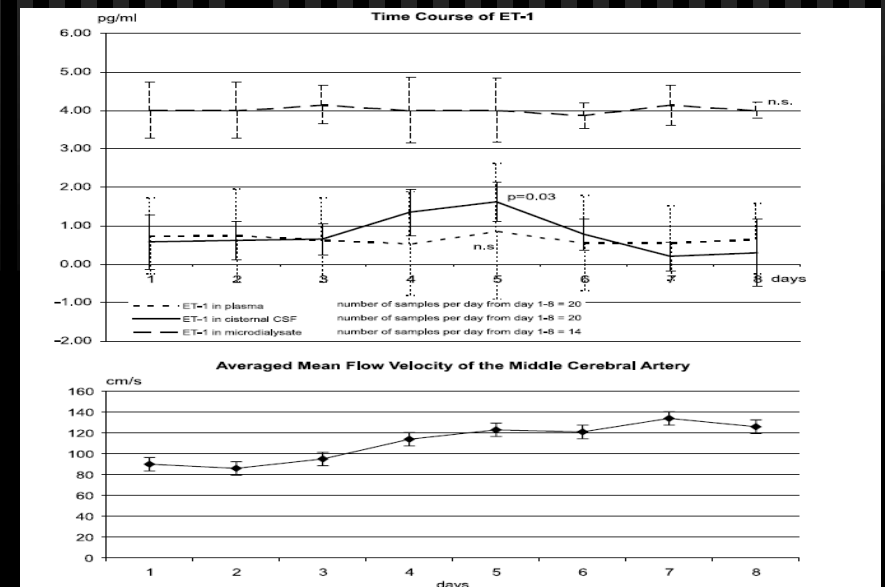


Fig. 2. Shows the time course of ET-1 in different sources. The p-value indicates that a significant change occurred within the time series of ET-1 in CSF. (Friedman ANOVA) Note that only ET-1 in CSF showed a significant increase on day 4 and 5 after subarachnoid hemorrhage

[Kastner S, et al. Acta Neurochir \(Wien\) 2005;147: 1271-1279](#)

# Endothelin Antagonist

- 2 types of ET-a receptors (ET<sub>A</sub> and ET<sub>B</sub>) are expressed in human cerebral arteries
  - Activation of ET<sub>A</sub> receptor induces vasoconstriction
  - Activation of ET<sub>B</sub> receptor mediates vasodilation

Nilsson I , et al. *Neurosurgery* 1997;40:346-351

- Clazosentan (AXV-034343), a selective endothelin A receptor antagonist, reduced frequency & severity of angiographic cerebral vasospasm (40% vs 88%) in 32 SAH patients (also lower incidence of infarctions 15% vs 44%)

Vajkoczy P, et al. *J Neurosurg* 2005; 103:9–17

- CONSCIOUS-1 trial found a significant reduction in rate of angiographic vasospasm in a dose-dependent manner but no improvement in clinical outcomes with clazosentan

Macdonald RL, et al. *Stroke* 2007;38:a453-a607

# Pharmacologic Clot Removal

## Intracisternal Thrombolysis

- Meta-analysis of all controlled trials in 652 patients
  - Absolute RR of 14.4% ( $P < 0.001$ ) for DIND
  - Absolute RR of 9.5% ( $P < 0.01$ ) for poor GOS
  - Absolute RR of 4.5% ( $P < 0.05$ ) for death
  - Effects did not differ based upon thrombolytic agent used (rt-PA vs. urokinase) or method (intraop vs. postop)
  - Studies enrolling pts at highest risk for vasospasm demonstrated greater treatment effects
  - Analysis limited by predominance of nonrandomized studies

# Nicardipine Prolonged Release Implants

- Nonrandomized cohort of 97 patients (69 with placement of subarachnoid pellets w/in 72 hrs of onset)
  - Dose range 8-40 mg of nicardipine
  - DIND developed in 6% of nicardipine pts vs. 11% of untreated pts
- Randomized Phase IIa study in 32 patients (16 received implants)
  - Incidence of angiographic vasospasm significantly reduced (7% vs 73%)
  - Lower incidence of DIND (14% vs 43%)
  - Significantly lower mortality (6% vs 38%)

# Erythropoietin

## Rationale

- During cerebral ischemia
  - ↑ EPO in astrocytes
  - ↑ EPO-R in neurons (stimulates endothelial NOS)
  - EPO enhances ischemic preconditioning, ↓ neuronal & vascular stem cell apoptosis, ↑ neurogenesis/angiogenesis
- Single dose systemic EPO found to normalize cerebral autoregulation after SAH
- Lower Hb levels are associated with worse outcomes regardless of SAH severity or the development of vasospasm
- No difference in outcome was seen in 73 SAH patients randomized to EPO (500 IU/kg/day x 3 days) or placebo

Bottiger BW, et al. Lancet 2001;357:1583-5

Ehrenreich H et al. Mol Med 2002;8:495-505

Springborg JB, et al. Br J Pharmacol 2002; 135: 823-9

Kramer AH, et al. Neurocrit Care 2008; Dec 31 [Epub]

Springborg JB, et al. Acta Neurochir (Wien) 2007;149:1089-1101

# Ongoing Clinical Studies

Intervention	Planned Size	Estimated Completion	Primary Outcome
EPO 40,000 U QD x3d vs. placebo	20	Sept 2008	Safety of 3d EPO (2° evaluate incidence of vasospasm)
Albumin 25% (4 dosing tiers)	80	Jan 2010	Safety & tolerability and functional outcome
Simvastatin 80 mg/d vs placebo x21d	60	March 2013	CBF & cerebral autoregulation during peak period of vasospasm
Magnesium infusion 16gm/d within 96 hrs x 20d vs. placebo	1200 (Phase III)	June 2012	mRS at 3 mo
Magnesium infusion 5gm bolus 20gm/day vs. placebo (IMASH) target Mg 2.0-2.5 mmol/L	340 (Phase III)	May 2009	Extended GOS at 6mos
Clozasantan 5mg/h vs placebo x 14d (CONSCIOUS-2)	765 (Phase III)	June 2009	Vasospasm related morbidity & mortality at 6 wks
Simvastatin 40 mg vs placebo up to 21d (STASH)	1600 (Phase III)	June 2011	mRS at 6 mos

[www.clinicaltrials.gov](http://www.clinicaltrials.gov) accessed Jan 22, 2009

# Present and Future Treatment Interventions





Evidence Based Discussion

# “Triple-H Therapy”

## Rationale

### ■ What is “Triple-H” therapy?

- Hemodilution HCT 30-35 
- Hypervolemia CVP 10-12 
- Hypertension SBP > 160 

Controversial- can result  
In ↓ O<sub>2</sub> delivery

Most widely used  
applications

### ■ Rationale based upon Poiseuille’s law

$$Q = (\Delta P \pi r^4) / (8)(L)(n)$$

Where Q = blood flow

ΔP = pressure change

r = vessel radius

L = length

n = viscosity

} Fixed Variables

Only variables that can be  
manipulated to improve blood flow  
are the pressure gradients &  
viscosity

# “Triple-H Therapy”

## Considerations

- Risks = heart failure, pulmonary edema (17%), dilutional hyponatremia (3%), cerebral edema (2%), increased ICP, rebleeding
- Remains most widely used medical therapy for vasospasm despite the lack of randomized controlled trials
  - 1st described in 1976 by Kosnik and Hunt who used phenylephrine and colloids in 7 pts to reverse neurological deficit associated with delayed vasospasm

# “Triple-H Therapy”

## Literature Review of Treatment

Study	N	Hyperdynamic Therapy	Study Endpoint	Outcomes
Kassell et al. Neurosurgery 1982	58	Hypervol: CVP=10, PCWP=18-20 HTN: SBP 150-240	DIND AE	Improvement 74% Unchanged 16% Deteriorated 10% Pulm Edema 17% Rebleed 10%
Awad et al. Stroke 1987	42	Hypervol: CVP10-12; PCWP 15-18 HTN: SBP 160-200 Hemodilution: Hct 33-38	Neurological deficit AE	Normal 47.6% Minor deficit 33.3% Major deficit 19% Cardiopulmonary complications 7%
Mori et al. Stroke 1995	51	Hypervol; albumin 3L/day Hemodilution: Hct 29-32	CBF DIND	No difference in CBF Normal 57% Mild-mod disability 15% Dead 15%

# “Triple-H” Therapy

MAP Goal > 130mm Hg with NE

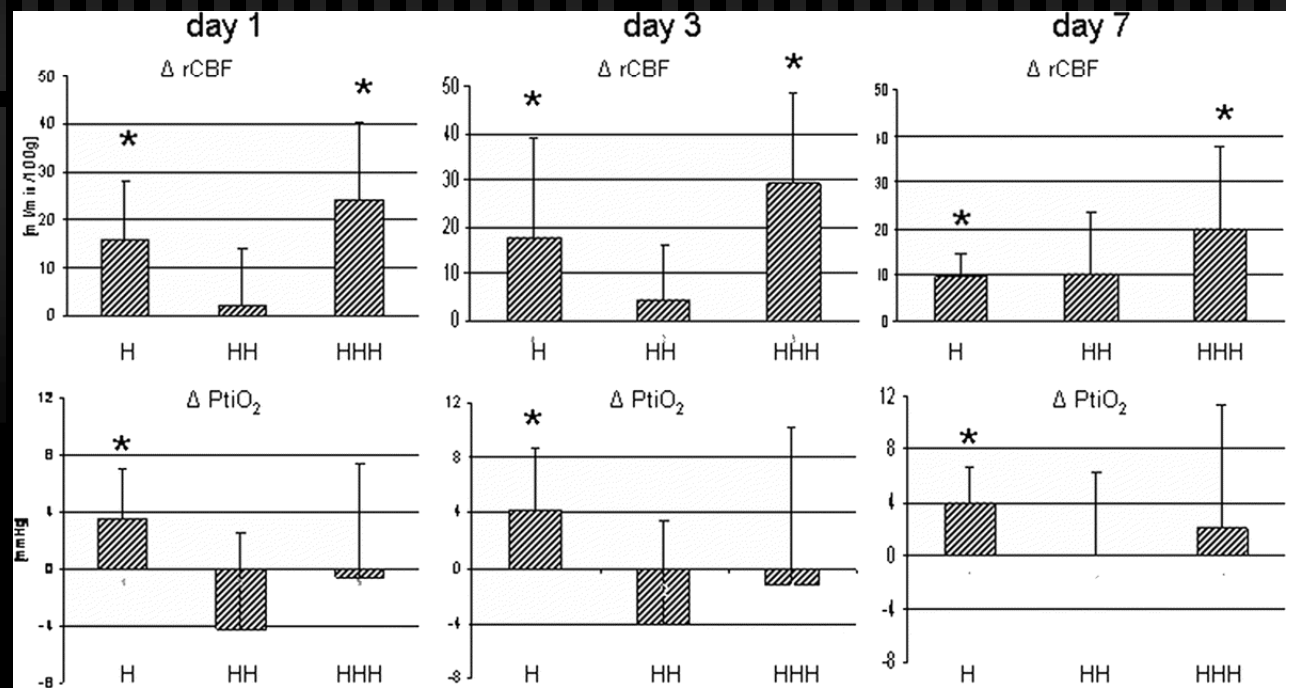
Hydroxyethyl-starch (1L) + crystalloids (1-3L) to achieve ITBVI > 1000 ml/m<sup>2</sup>

Hemodilution passively achieved with volume & repeated blood draws

Induced HTN resulted in significant ↑ in rCBF and brain tissue oxygenation

Induced hypervolemia/hemodilution resulted in slight ↑ rCBF and no improvement in brain tissue oxygenation

Triple-H failed to improve rCBF more than HTN alone and reversed the effect on brain tissue oxygenation



Muench E, et al. Crit Care Med 2007;355:1844-1851

# “Triple-H Therapy”

## Literature Review of Prophylaxis

Study (year)	Study Groups	N	Outcome
Lennihan et al. (2000)	Hypervolemia Normovolemia	41 41	No difference in mean global CBF, minimal regional CBF, or symptomatic spasm 14 & 90-day outcomes similar
Egge et al. (2001)	Hypervolemia Normovolemia	16 16	No difference in vasospasm (clinical or radiographic) or CBF No difference in 1-year outcomes ↑ Costs and complications for hyperdynamic group

- Review of controlled trials concluded there was no evidence of benefit but the risk of death was higher (RR 0.68, 95% CI 0.53-0.87)

Lennihan L, et al. Stroke 2000; 31:383-391  
Egge A, et al. Neurosurgery 2001; 49:593-605  
Treggiari MM, et al. J Neurosurg 2003;98:978-84

# Cardiac Output Augmentation

- It has been postulated that wider pulse pressure and enhanced pulsatile flow associated with inotropic agents may ameliorate flow through collateral vessels and through microvasculature
- Augmentation of CO has been accomplished using dobutamine and milrinone
  - Use of dobutamine has been associated with a 52% ↑ CO & clinical reversal of ischemic symptoms in 78% of pts treated
  - Similar ↑ in CBF has been observed between dobutamine and phenylephrine
  - Milrinone has been shown to have a more potent ↑ CO & SV but also more potent ↓ SVR & SBP than dobutamine
- Further study needed to understand the effects of ↑ CO on CBF and reversal of vasospasm

Naval NS, et al. Crit Care Med 2006;34:511-524  
Naidech A, et al. Neurosurgery 2005;56:21-61  
Levy ML, et al. J Neurosurg 1993;79:494-499  
Kim D, et al. Neurosurg 2003;53:1044-1051

# Albumin



- Human albumin might be useful to promote volume expansion in patients who fail to achieve hypervolemia with NSS
- Retrospective study found the incidence of VSP was similar in albumin and non-albumin treated patients
  - After controlling for injury severity, albumin administration was independent predictor of improved 3-month outcome
- Multicenter trial (ALISAH) testing different doses of albumin is underway

# Endovascular Treatment Options

## ■ Transluminal balloon angioplasty

- Reversal of DIND in 30-70% in large proximal conducting vessels
- Most effective when used within 2 hr of ischemia onset
- Risks = vessel occlusion, vessel rupture, thrombus formation, aneurysm clip displacement
- Study currently evaluating prophylactic use

## ■ Intra-arterial vasodilators

- Useful for distal vessel vasospasm not amenable to angioplasty
- Agents utilized = papaverine, verapamil, nicardipine
- Clinical response varies 20-50%
- Papaverine use limited by AE (increased ICP, seizures, rebound vasospasm, neurotoxicity, systemic hypotension)

# Endovascular Treatment

## Reviews of Clinical Reports

### ■ Papaverine (nonselective inhibitor of phosphodiesterase)

- Clinical improvement in 43% of patients only transiently (<24hrs)
- 42% require multiple treatment & 29% eventually require angioplasty
- Significantly improved mean CBFV but only for < 48 hours
- Improved CBF in 60% but only for < 12 hours
- Associated with increases in ICP (9.9% complication rate)

### ■ Nicardipine (0.5-22 mg)

- Clinical improvement in 42%
- Significantly improved mean CBFV lasted 4 days
- No complications (although another report found transient ↑ ICP)

### ■ Verapamil (average 3 mg/patient)

- Clinical improvement reported in 29.4%
- No complications

Hoh BL, et al. Neurosurg Clin N Am 2005;16:501-16  
Badjatia N, et al. Am J Neuroradiol 2004;24:819-26  
Brisman JL, et al. Neurol Res 2006;28:769-776

# Endovascular Treatment

## Reviews of Clinical Reports

### Phosphodiesterase III Inhibitors

Study	Intervention	N	Outcome
Arakawa Y, et al. Neurosurgery 2001;48:723-8	Milrinone IA 2.5-15 mg + IV milrinone 0.5-0.75 µg/kg/min up to 2 wks	7	Dilation of vasospastic vessel in all patients; ↑ CBF; recurrence 3/7
Romero CM, et al. Neurocrit Care 2008 Jan 18 [Epub]	Milrinone IA 10-15 mg	8	All patients showed angiographic response; recurrence 3/8
Fratlicelli AT, et al. Stroke 2008;39:893-8	Milrinone IA 8mg over 30min + IV milrinone 0.5- 1.5 µg/kg/min until day 14	22	53.7% ↑ in arterial diameter; 23% had recurrence w/in 48hrs
Yoshida K, et al. AJNR AM J Neuroradiol 1997;18:492-6	Amrinone IA 3mg/kg	2	Mild reversal of vasospasm

# Intraventricular Nicardipine

- Prophylactic intrathecal administration of nicardipine
  - ↓ incidence of symptomatic vasospasm by 26%
  - ↑ in good outcome by 15%
  - AE = headache, nausea, hydrocephalus, infection
- Retrospective case series of 8 patients with refractory vasospasm
  - Intraventricular nicardipine (4 mg q 12hr) for a total of 5-17 days
  - 7 patients had moderate-good outcome (6 went home)
  - No AE

Shibuya M, et al. *Acta Neurochir (Wein)* 1994;131:19-25  
Suzuki M, et al. *Neurosurg Rev* 2001;24:180-4  
Godson K, et al. *Neurocrit Care* 2008;8:247-252

# Nitric Oxide Donors

## ■ Rationale

- Multiple animal studies with NO induction demonstrated a significant effect on CBF
- Administration of NO donors → resolution of cerebral vasospasm

## ■ Intrathecal and intraventricular administration of SNP

- Effective in reversing severe symptomatic vasospasm refractory to medical interventions
- Shown variable effects on cerebral hemodynamics and oxygenation

## ■ Transdermal NTG

- CBF ↑
- No difference DIND

Pluta RM, et al. J Neurosurg 1997;87:746-751  
Sebba FA, et al. J Neurosurg 2007;106:321-329  
Thomas JE, et al. Neurosurgery 1999;44:48-57  
Vajkoczy P, et al. Stroke 2000;31:1195-1197  
Raabe A, et al. Neurosurgery 2002;50:1006-1013  
Reinert M, et al. Neurol Res 2004;26:435-439

# Cerebral Vasospasm Treatment

## SAH Guideline Recommendation

- Treatment of cerebral vasospasm begins with early management of the ruptured aneurysm, and in most cases, maintaining normal circulating blood volume and avoiding hypovolemia are probably indicated (Class IIa, Level of Evidence B)
- One reasonable approach to symptomatic cerebral vasospasm is volume expansion, induction of hypertension, and hemodilution (triple-H therapy) (Class IIa, Level of Evidence B)
- Alternatively, cerebral angioplasty and/or selective intraarterial vasodilator therapy may be reasonable after, together with, or in place of triple-H therapy, depending on the clinical scenario (Class IIb, Level of Evidence B)

# Summary



- Vasospasm continues to adversely affect a significant proportion of SAH population
- Many “tried and true” methods of prophylaxis/treatment of vasospasm are not based on strong evidence
- There is a need for more evaluation of both the current and future interventions

# Comparison of Evidence

Author	Year	Therapy	N	Outcome Assessed
Lennihan	2000	HHH	82	Incidence of VSP
Egge	2001	HHH	32	Incidence of clinical VSP
Vajkoczy	2005	Clazosentan	40	Incidence of VSP
Van den Bergh	2005	Mg <sup>2+</sup>	283	Ischemic lesion 3 mos
Veyna	2000	Mg <sup>2+</sup>	40	Incidence of clinical VSP
Boet	2005	Mg <sup>2+</sup>	45	Incidence of VSP
Ohman	1991	Nimodipine	213	Poor outcome 1-3yrs
Jan	1988	Nimodipine	188	Poor outcome at discharge
Pickard	1989	Nimodipine	554	Incidence of cerebral infarction
Tseng	2005	Pravastatin	80	Incidence of VSP
Lynch	2005	Simvastatin	39	Incidence of clinical VSP
Findlay	1995	rt-PA	91	Angiographic VSP

