CURRENT PROGRESS IN PREVENTION AND TREATMENT OF DELAYED CEREBRAL VASOSPASM (DCV)

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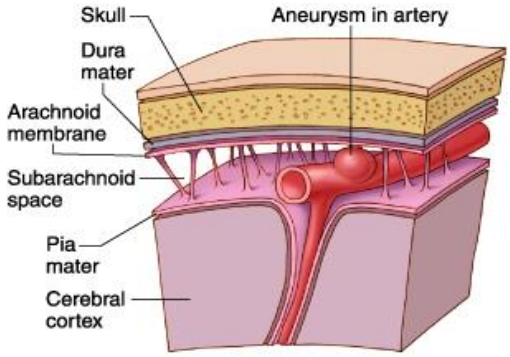

Ministry of health

LIST OF ABBREVIATIONS AND ACRONYMS

CSF Cerebrospinal fluid
CT Computed tomography
DCI Delayed cerebral ischaemia
EPO Erythropoietin
EEG Electroencephalography
GCS Glasgow Coma Scale
GOS Glasgow Outcome Scale
IV Intravenous
RCT Randomised controlled trial
SAH Subarachnoid haemorrhage
SPECT Single Photon Emission Computed Tomography
TCD Transcranial Doppler
US Ultrasound

Abstract

In patients who suffer a subarachnoid haemorrhage, the greatest risk of mortality and morbidity is in those who go on to develop delayed cerebral vasospasm. There are currently no British guidelines for prevention and management of this complication, with treatment varying between centres. This review aims to evaluate the current progress in prevention and treatment research, including novel therapies. Most good quality clinical trials have focused on prevention, supporting the use of triple H therapy and calcium channel blockers for prophylaxis. There is also some evidence for other medications, for example tirilazad and magnesium, although further research may be needed to demonstrate any benefit over and above that achieved with other more commonly used preventive measures. Less research is available on treatments to reverse vasospasm once it has begun, although at present balloon angioplasty and calcium channel blockers seem to remain the best supported, enabling some reversal of constriction. However, as this is a complex pathophysiological process, there are many potential targets for therapy, and as our understanding of this improves, novel therapies which can improve the outlook for these patients are likely to be developed.

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1. Introduction

In the UK, there is an estimated incidence of subarachnoid haemorrhage (SAH) of 9.7 per 100,000 person-years. This is a serious condition, with fatality estimated at 21% with 24 hours and 44% at 1 month post-SAH (Pobereskin, 2001, p. 340). It is cerebral vasospasm, or tightening of the vessels within the brain in response to the bleed, which is the leading cause of death and disability afterwards (Kassell *et al.*, 1985, p. 562). Estimates of the proportion of patients developing vasospasm vary between 16% and 70%; this is largely dependent on how vasospasm is defined, whether based on clinical signs, radiology or objective physiological measurement (Kassell *et al.*, 1985, 563; Frontera *et al.*, 2009, p. 1963). The risk of developing delayed ischaemic neurological deterioration, through ischaemia and infarction, is as high as 50% in those who have angiographic vasospasm (Macdonald *et al.*, 2007, p. 256; Bulsara *et al.*, 2014, p. 1).These figures demonstrate that this represents a significant issue for those working in neurology and intensive care medicine.

However, at present, the outcomes for patients seem to be highly variable, depending on how their vasospasm is treated, and whether prophylactic measures are taken early on in SAH management. This is because there is currently no standardised practice approach for prevention and management of delayed cerebral vasospasm (Bulsara *et al.*, 2014, p. 1). Although there have been a number of previous reviews which have sought to summarise the evidence on prevention and treatment of delayed cerebral vasospasm (Castanares-Zapatero & Hantson, 2011, pp. 1-12; Sehba *et al.*, 2011, p. 27; Velat *et al.*, 2011, pp. 446-454), these reviews seem to be missing a number of key studies, focusing on some of the treatments that have been investigated at the expense of others. Therefore this review seeks to summarise the evidence which is currently available on prevention and treatment of delayed cerebral vasospasm in patients after SAH.

The research question which this review aims to address is:

How effective are current approaches towards prevention and treatment of delayed cerebral vasospasm after subarachnoid haemorrhage and what progress is currently being made in this area?

In order to address this question, there are some issues associated with the diagnostic process and pathophysiology of the condition which are important. Therefore the next two chapters present a brief discussion on each of these issues in turn. The review then examines the evidence for different preventive treatments, followed by therapeutic treatments, finally considering some of the novel interventions which are currently being researched.

2. Diagnosis

The methods used to predict and diagnose delayed cerebral vasospasm in clinical practice are likely to influence patient outcome, as its sensitivity and specificity will determine whether appropriate treatment is given to the patient (Harrod *et al.*, 2005, p. 633; Greenberg *et al.*, 2010, p. 1853).The methods used to define cerebral vasospasm are also an important consideration when evaluating research on prevention and treatment of vasospasm, as the methods used could influence study outcome. This chapter therefore discusses the definitions of delayed cerebral vasospasm commonly used, along with predictive and diagnostic approaches towards identifying patients at risk.

2.1 Definition of Delayed Cerebral Vasospasm

Kassell *et al.* (1985, p. 563) identify two distinct definitions of cerebral vasospasm: clinical and angiographic cerebral vasospasm. Angiographic vasospasm was first described in the 1950s (Ecker & Riemenschneider, 1951, p. 660) and is defined by the observed narrowing of the major cerebral arteries, inferred from the reduced passage of dye through the lumen (Kassell *et al.*, 1985, p. 563).This has always been the gold standard for diagnosis (Carr *et al.*, 2013, p. 2), although there can be difficulties, due to anatomical differences between patients (Kassell *et al.*, 1985, p. 563).)There are also risks inherent to this diagnostic procedure, along with high costs (Kassell *et al.*, 1985, p. 563). Newer techniques have been developed which reduce this risk, utilising CT technology, and have been shown to have high levels of diagnostic accuracy (Greenberg *et al.*, 2010, p. 1853), but may still require expertise and funding that is not available at all centres.

In contrast, clinical vasospasm is defined by Kassell *et al.* (1985, p. 563) as a syndrome of clinical symptoms which have resulted from ischemia due to cerebral arterial narrowing. The symptoms include confusion of insidious onset, followed by a decreased consciousness level and focal deficits in speech and motor function. Patients will also often complain of headache and demonstrate an increased blood pressure. Frontera *et al.* (2009, p. 1963) suggest that in the absence of radiographic imaging, this clinical deterioration may only be attributable to cerebral vasospasm once other causes have been excluded.

Frontera *et al.* (2009, p. 1963) expand on earlier cerebral vasospasm work to include two further definitions. The first of these is described as delayed cerebral ischemia, which is defined similarly to

symptomatic vasospasm, but is observable on computed tomography (CT). The second is transcranial Doppler (TCD) spasm, which is defined according to a flow velocity of more than 120cm/s (Frontera *et al.*, 2009, p. 1963).

Both angiographic and clinical vasospasm usually becomes evident from around the 4th day post-haemorrhage, peaking at around the 7th day (Kassell *et al.*, 1985, p. 563). This is due to the time course over which the physiological changes causing vasospasm develop (Sehba *et al.*, 2011, p. 28).It is estimated that between 40% and 70% of those suffering from subarachnoid haemorrhage will demonstrate some degree of angiographic vasospasm by the 7th day post-haemorrhage, while around 20% to 30% of patients will develop clinical vasospasm (Kassell *et al.*, 1985, p. 563). Even considering newer technologies, clinical symptoms of vasospasm do not always directly correlate with objectively measurable ischemia. For example, Darby *et al.* (1994, p. 857) found that in a sample of 13 patients, only 54% had reversible ischemia identifiable on xenon-enhanced CT, although this could potentially be related to the cut-off used to define ischemia.

It is clinical vasospasm which is most associated with clinical outcomes, including quality of life (Frontera *et al.*, 2009, p. 1963). Therefore despite angiography being the gold standard for diagnosis (Carr *et al.*, 2013, p. 2), it is clinical vasospasm which should be the focus of diagnosis and research.

2.2 Diagnosis of Cerebral Vasospasm in Clinical Practice

As Dorsch (2002, p. 128) highlights, there is risk associated with any intervention designed to prevent or treat vasospasm. Therefore it would be desirable to have some method for detecting those patients at greatest risk of vasospasm, so that interventions can better be targeted. It would seem that in the U.S., most clinicians screen for cerebral vasospasm routinely, with 70.1% of respondents reported using daily transcranial Doppler ultrasounds (TCDs) for this purpose. Others commonly reported using routine CT (figure1) angiography or a routine angiography between days 5 and 10 post-haemorrhage. Other techniques which were reported in the survey were CT or xenon perfusion studies, SPECT or continuous EEG monitoring. There is less information available on the screening tools chosen in the UK, but it would be expected to be similar based on the availability of all of these methods.

Figure 1: CT scan showing subarachnoid hemorrhage (blood in white) (Hunt We *et al* p.17)

There has also been some interest in the literature regarding more simple methods of screening patients, based on physiological variables that seem to be correlated with vasospasm. However, most of the methods which have been described are not sufficiently effective to provide a single screening tool. For example, vasospasm is more likely in patients who present with poor neurological status (Dorsch, 2002, p. 128); however they are not the only patients to develop vasospasm, so relying on this alone would lead to some patients going untreated. A sudden increase in cerebral blood flow velocity, as measured by TCD may predict onset of spasm; however, this may also be due to hyperemia and is operator dependent (Dorsch, 2002, p. 128).

Hypomagnesemia has been shown to correlate with delayed cerebral ischaemia (DCI) and may therefore be used to predict this (Castanares-Zapatero & Hantson, 2011, p. 3), but again, is insufficient alone as not all patients who develop vasospasm have low magnesium. Even combining these predictive factors into a single indices is only partially effective. One such index based on TCD velocity increase, GCS score , presence of carotid/anterior cerebral artery aneurysms and clot thickness was still only 68% sensitive (Qureshi *et al.*, 2000, p. 984).

Yokose *et al.* (2010, p. 508) found a reduction in cortical oxygen saturation around the middle cerebral artery was shown to have 100% sensitivity and 85.7% specificity with values of 3.9% to 6.4%.

However, this was based on only a small sample of 14 patients.

The conclusion based on this is therefore that it would be more appropriate in the absence of an effective screening tool to offer prophylactic treatment to all patients who suffer from SAH, based on the severity of complications which this is associated with. However, to understand the mechanisms of the therapies available for prophylaxis, it is also necessary to understand the pathophysiology of vasospasm.

3. Pathophysiology

There are a number of key authors in this area who were pioneering in reviewing the pathophysiology of cerebral vasospasm, such as Weir (1995, p. 375) and Carr *et al.* (2013, p. 1) and a full discussion of the pathophysiology is a paper in itself. Therefore this chapter merely summarises some of the main theories which are relevant to later discussions on therapy.

The main issue in cerebral vasospasm is that neurological damage is caused by reduced minimum cerebral blood flow as the arteries narrow (Touho *et al.*, 1992, p. 671; Muizelaar & Becker, 1986, p. 317; Mori *et al.*, 1995, p. 1620; Lennihan *et al.*, 2000, p. 383) . The criticalvalue of 20ml/100mg/min was identified by Touho *et al.* (1992).However, the question of importance is what it is that causes this to happen.

One theory is that this could be mechanical, with arteries compressed by the clot (Kassell *et al.*, 1985, p. 563; Sehba, 2011, p. 28). However, vasospasm most likely in the period 5 to 7 days after SAH (Dorsch, 2002, p. 128), it is now thought that it is the first 72 hours after SAH during which the important damage occurs (Sehba *et al.*, 2011, p. 27). Touho *et al.* (1992, p. 671) noted dysautoregulation in all patients with angiographic vasospasm, although only 8 of 20 patients developed clinical vasospasm, which suggests that something other than dysfunctional autoregulation determines whether clinical symptoms are experienced.

The presence of clots in an area of the brain seems to correlate well with the subsequent development of vasospasm in that same area (Fisher *et al.*, 1980, p. 1). This therefore seems to lend support to the theory that vasoactive substances released from clots play a role in the vasospasmodic process (Castanares-Zapatero & Hantson, 2011, p. 4). Some of the substances which are released as a result of SAH are powerful vasoconstrictors, such as endothelin (Zimmerman & Seifert, 1998, p. 863). However, experiments in animal models have shown no association between endothelin levels and vasospasm (Pluta *et al.*, 1997, p. 287).

It is also possible that increasing tissue oxygenation could in itself further exacerbate vasospasm. Calcium-activated potassium channels become activated under depolarisation and cause vasoconstriction (Zhang & Cook, 1994, p. 327). Oxyhaemoglobin, as is present in the blood leaked in SAH, reduces potassium channel activity through enhancing tyrosine kinase activity and increased voltage-dependent calcium channel expression. ATP-dependent potassium channels are activated by neuropeptides and other substances and lead to vasodilation (Zhang & Cook, 1994, p. 327). Therefore their blocked action could potentially lead to depolarisation and therefore vasoconstriction (Ishiguro *et al.*, 2006, p. 1252; Link *et al.*, 2008, p. 2122). This is not the only pathophysiological change, as features other than arterial smooth muscle contraction are observed in vasospasm (Asano, 1999, p. 303).

A link between cerebral vasospasm and inflammation was first made over 60 years ago (Carr *et al.*, 2013, p. 2).This is supported by research with animal models, where SAH has been shown to be associated with vasospasm on the clot side, most often in the extradural internal carotid artery, intradural internal carotid artery, precommunicating segment of the anterior cerebral artery and the middle cerebral artery (Kanamaru *et al.*, 1990, p. 29). However, it is now recognised that this is a very complex process, with interaction of many different factors, and it has become increasingly clear in recent years that cell signalling pathways are one of the critical mechanisms in the pathophysiology of cerebral vasospasm after SAH (Zubkov *et al.*, 2003, p. 47).

When inflammation occurs in response to the vessel damage, this is likely to lead to high circulating levels of immune complexes, such as IgG and complement (Kassell *et al.*, 1985, p. 563). However, the main mechanism seems to be associated with leukocyte-endothelial cell interactions at the site of the damage (Chaichana *et al.*, 2010, p. 22). The inflammatory process causes a number of vasoactive substances to be released, some of which cause constriction, such as prostacyclin and thromboxane A2. These, along with others, impair vasodilation, for example the oxyhaemoglobin which would be found in blood leaking in SAH (Kassell *et al.*, 1985, p. 563). In addition to oxyhaemoglobin's effect, haemoglobin in cerebrospinal fluid (CSF) is metabolised to form bilirubin, which in turn leads to generation of bilirubin oxidation products. This increases oxidative stress which could also lead to vasospasm. This is supported by a study which showed that these two substances were significantly higher in CSF from patients after vasospasm (Pyne-

Geithman *et al.*, 2005, p. 1070), although this was based only on 12 patients. A further pathological changes suspected of contributing to delayed cerebral vasospasm is the depletion of nitric oxide in cells surrounding the SAH. Nitric oxide is an important vasodilator, therefore deficiency leads to insufficient vessel relaxation (Castanares-Zapatero & Hantson, 2011, p. 4). This deficiency is due to a combination of both nitric oxide synthase dysfunction and scavenging of nitric oxide by deoxyhaemoglobin (Fathi *et al.*, 2011, p. 93).It has recently come to light that there could also be a role for genetic susceptibility, with some alleles found more commonly in those who go on to develop vasospasm (Lanterna *et al.*, 2007, p. 766; Olivecrona & Koskinen, 2012, p. 675).

The evidence presented by different studies to support various different pathophysiological processes suggests that this is most likely a complex process, with many different elements. Therefore therapies may need to address these different aspects simultaneously. The next chapter examines some of the major prophylactic therapies which are currently available for SAH patients to prevent vasospasm.

4. Prevention

Most of the treatments for delayed cerebral vasospasm which have been examined in the literature have focused on prevention in SAH patients. Although there is some debate as to the level of effect this has on clinical outcome (Etminan *et al.*, 2011), it would be assumed that it would be preferable to intervention once established, given the high degree of pathological changes that would have already occurred at that time (Sehba *et al.*, 2011, p. 28). Table 1 below summarises the key studies which are currently available in this area. Each different category of intervention is then discussed in further detail.

Table 1: Studies examining the effect of interventions for prevention of delayed cerebral vasospasm

Author	Intervention	Study Design	Sample	Incidence of vasospasm	Main Findings
Suzuki *et al.* (1989)	Thromboxane synthetase inhibitor 80mg and 400mg	Multicentre, double-blind randomised controlled trial (RCT)	Sample from 48 centres	NA	Significantly reduced incidence of vasospasm in 80mg treatment compared to placebo Faster improvement in those receiving 400mg treatment compared to placebo
Shibuya *et al.* (1992)	Fasudil hydrochloride 30mg	Double-blind RCT	276 patients	Angiographic Placebo: 61% Treatment: 38% CT Placebo: 38% Treatment: 16% Clinical Placebo: 26% Treatment: 12%	Significantly reduced angiographic vasospasm (p = .0023), vasospasm demonstrable on CT (p = .0013) and symptomatic vasospasm (p = .0152)
Haley *et al.* (1993)	Nicardipine 0.15 mg/kg/hr	Double-blind, multicentre RCT	906 patients from 41 centres	Clinical Placebo: 46% Treatment: 32%	Significantly reduced incidence of clinical vasospasm (p < .001) Outcomes were similar at 3 months
Kassell *et al.* (1996)	Tiralazad mesylate 0.6 or 2 or 6mg/kg/day	Double-blind, multi-centre RCT	1023 patients from 41 centres	NA	Reduced mortality with 6mg/kg (p = 0.01) at 3 months Better recovery in 6mg/kg (p = .01) at 3 months No significant reduction in symptomatic vasospasm (p = .048) in first 14 days
Haley *et al.* (1997)	Tiralazad mesylate 2 or 6mg/kg/day	Double-blind, multi-centre RCT	902 patients from 54 centres		No significant difference in incidence or severity of symptomatic or angiographic vasospasm No significant difference in mortality or recovery at 3 months, except in males with

					higher grade admission neurology (p = .03)
Saito *et al.* (1998)	Ebselen 150mg twice daily	RCT	286 patients	Clinical Placebo: 41.1% Treatment: 35.8%	Significantly reduced development of ischaemic deficit in patients with treatment (p = .005)
Lanzino *et al.* (1999)	Tirilazad mesylate 15 mg/kg/day	Double-blind, multi-centre RCT	819 women in 56 centres	Clinical Placebo: 33.7% Treatment: 24.8%	No significant difference in mortality rate or clinical outcome; this held across different stratified groups Lower incidence of symptomatic vasospasm in treatment group (p = .005) Lower severity of vasospasm in the treatment group (p = .008) Lower rate of cerebral infarction in treatment group (p < .04)
Lanzino & assell (1999)	Tiralazad mesylate 15mg/kg/day	Double-blind, multi-centre RCT	823 women from 65 centres	Clinical Placebo: 38% Treatment: 35%	No significant difference in mortality, except for males with higher grade neurology on admission (p = .016) No significant difference in clinical outcome between groups except in those with lower grade neurology on admission, who had better outcomes on placebo (p = .04) No significant difference in incidence or severity of symptomatic vasospasm
Shaw *et al.* (2000)	TAK-044 (endothelin receptor antagonist)	Double-blind, multicentre RCT	420 patients from 20 centres	Clinical Placebo: 36.6% Treatment: 29.5%	Lower incidence of delayed ischaemia in the treated group, although this was not significant No significant difference in clinical outcomes between groups
Egge *et al.* (2001)	Triple H therapy	RCT	32 patients	Clinical Placebo: 45.4% Treatment: 33.3%	No significant difference in incidence of clinical vasospasm
Papavasiliou *et al.* (2001)	Oral diltiazem	Observational study	123 patients	NA	Incidence of delayed ischaemic neuroligic deficit was 19.5%
van den Bergh *et al.* (2002)	Magnesium sulphate 64 mmol/day	RCT	283 patients	Clinical Placebo: 16% Treatment: 24%	The risk of delayed cerebral aneurysm was reduced by 34% There were more patients in the treatment group who were evaluated as having an excellent clinical outcome
Veyna *et al.* (2002)	Magnesium sulphate – titrated to patient	Single blind RCT	40 patients	Angiographic Placebo: 31% Treatment: 30%	Symptomatic vasospasm, confirmed on angiography, were similar in both groups Clinical outcomes were similar in both groups There were no adverse events
Hamada *et al.* (2003)	Urokinase	RCT	110 patients	Clinical Placebo: 30.2% Treatment: 8.8%	Significant reduction in vasospasm (p = .012) Significantly better outcomes (p = .036) No difference in mortality

Amin-Hanjani *et al.* (2004)	Thrombolytics	Meta-analysis	9 studies	NA	Absolute risk reduction of 14.4% ($p < .0001$) for delayed cerebral ischaemia Absolute risk reduction of 9.5% ($p < .01$) for poor GCS Absolute risk reduction of 4.5% ($p < .05$) for death
Suarez *et al.* (2004)	Albumin	Retrospective notes review	140 patients	Clinical No albumin: 28% Albumin: 19%	Less vasospasm in those who received albumin, although this was not significant ($p = .2$)
Wurm *et al.* (2004)	Enoxaparin	Double-blind RCT	120 patients	Clinical Placebo: 66.7% Treatment: 8.8% Angiographic Placebo: 47.7% Treatment: 15.8%	Significant reduction in ischemic deficit ($p < .001$) No significant reduction in diffuse angiographic vasospasm ($p = 1.0$), but in local there was ($p = .002$)
Kasuya *et al.* (2005)	Nicardipine prolonged-release implants	Observational study	125 patients	Clinical Placebo: 11% Treatment: 6%	Reduced incidence of delayed cerebral ischaemia associated with nicardipine
Lynch *et al.* (2005)	Simvastatin 80mg/day	RCT	39 patients	Clinical Placebo: 60% Treatment: 26%	Vasospasm significantly lower in treatment group ($p < .05$) TCA velocities significantly lower in treatment group ($p < .01$)
Tseng *et al.* (2005)	Pravastatin 40mg/day	RCT	80 patients	Clinical Placebo: 62.5% Treatment: 42.5%	Vasospasm and severe vasospasm both reduced in treatment group ($p = .006$ and .044 respectively) The duration of vasospasm was reduced by 0.8 days in treatment group Mortality was reduced by 75% ($p = .037$)
Vajkoczy *et al.* (2005)	Clazosentan 0.2 mg/kg/hr (endothelin receptor antagonist)	Double-blind, multicentre RCT	32 patients	Clinical Placebo: 88% Treatment: 44%	Significant reduction in risk of vasospasm in treatment group ($p = .008$) Severity of vasospasm reduced in treatment group ($p = .012$)
Wong *et al.* (2006)	Magnesium sulphate 80 mmol/day	RCT	60 patients	Clinical Placebo: 43% Treatment: 23%	There was no significant difference in the incidence of vasospasm between groups ($p = .06$) The duration of vasospasm was longer in the placebo group ($p < .01$) but there was no difference in clinical outcome
Zhao *et al.* (2006)	Fasudil	RCT	65 patients	Clinical Placebo: 28% Treatment: 15%	Reduced incidence of vasospasm in treatment group Improved clinical outcomes in intervention group
Chou *et al.* (2008)	Simvastatin 80 mg/day	Double-blind RCT	39 patients	Angiographic Placebo: 40% Treatment: 26%	There was a reduced incidence of angiographically confirmed vasospasm in the treatment group
Kramer *et al.* (2008)	Simvastatin 80 mg/day	Retrospective chart review	150 patients	Angiographic Placebo: 42% Treatment: 41% Clinical Placebo: 25% Treatment: 32%	No significant differences in rates of angiographic vasospasm or symptomatic vasospasm No differences in clinical outcome between groups

Macdonald *et al.*(2008)	Clazosentan 1 or 5 or 15 mg/hr	Double-blind RCT	413 patients	Clinical (15mg/hr) Placebo: 66% Treatment: 23%	Significant reduction in vasospasm in the high-dose group ($p < .0001$) No effect on mortality
Muroi *et al.* (2008)	Magnesium sulphate titrated to the patient	RCT	58 patients	Clinical Placebo: 37% Treatment: 39%	No significant difference in incidence of vasospasm, although clinical outcome was better if adopting an on-treatment analysis
Kronvall *et al.* (2009)	Nimodipine	RCT	106 patients	Clinical Oral: 28% IV: 30%	No significant difference in delayed cerebral ischaemia
Tseng *et al.* (2009)	EPO 30 000 units	RCT	80 patients	Clinical Placebo: 40% Treatment: 27.5%	No significant difference in rate of vasospasm Decreased incidence of severe vasospasm in treatment group ($p = .037$)
Vergouwen *et al.* (2009)	Simvastatin 80mg/day	Double-blind RCT	32 patients	Clinical Placebo: 69% Treatment: 81%	There was no significant difference in incidence of vasospasm
Wong *et al.* (2010)	Magnesium sulphate titrated to patient	Multicentre RCT	327 patients	Clinical Placebo: 18% Treatment: 25%	No significant difference in incidence of vasospasm between groups No difference in clinical outcome after 6 months
Kirkpatrick *et al.* (2014)	Simvastatin 40 mg/day	Double-blind, multicentre RCT	803 patients	Clinical Placebo: 16% Treatment: 16% Radiographic Placebo: 17% Treatment: 16%	There was no significant difference between groups in symptomatic or radiological vasospasm

4.1 Triple H Therapy

Triple H therapy is the term used to describe the induction of hypertension, hypervolaemia and haemodilution after a patient has suffered a SAH (Lee *et al.*, 2006, p. 69). The careful control of these factors in the intensive care setting has been described since the 1970s, although there are relatively few clinical trials to evaluate the efficacy of this approach (Sen *et al.*, 2003, p. 614). Systematic reviews have revealed between 3 and 11 studies, depending on whether studies examining one or all three components were included (Dankbaar *et al.*, 2010, p. 1; Velat *et al.*, 2011, p. 446).

The rationale behind this treatment approach is based on the haemodynamic changes associated with delayed cerebral artery vasospasm. As the arteries in spasm narrow, vascular resistance is shifted to the vessels in the circle of Willis (figure2) and the area normally supplied by the penetrating arterioles develops dysfunctional autoregulation. As the radius of the artery has become fixed in spasm, the only way to improve blood flow is to alter blood viscosity and pressure gradient (Lee *et al.*, 2006, p. 69). Increasing blood flow should then theoretically increase oxygenation to brain tissue (Muench *et al.*, 2007, p. 1844). The focus of this approach in some studies has been very much on prevention of delayed cerebral vasospasm, with treatment initiated at the outset of care after SAH (Lennihan *et al.*, 2000, p. 383; Egge *et al.*, 2001, p. 593). However, in others, it has instead been targeted at treatment after onset of cerebral vasospasm (Ekelund *et al.*, 2002); these are discussed later in the review.

One of the earliest studies by Rosenwasser *et al.* (1983, p. 658) found that treating SAH patient with volume expansion and controlling hypertension, using a combination of vasodilators and centrally-acting antihypertensives, was associated with a significant reduction in preoperative vasospasm. Therefore this was not a triple H approach, including only two of the components. This led to 87% of the treated group surviving to surgery, as compared to 53% of the control group, who were treated with diuretics for hypertension control alone. However, subsequent studies have shown mixed results, possibly due to not including the blood pressure lowering component included by Rosenwasser *et al.* (1983, p. 658).

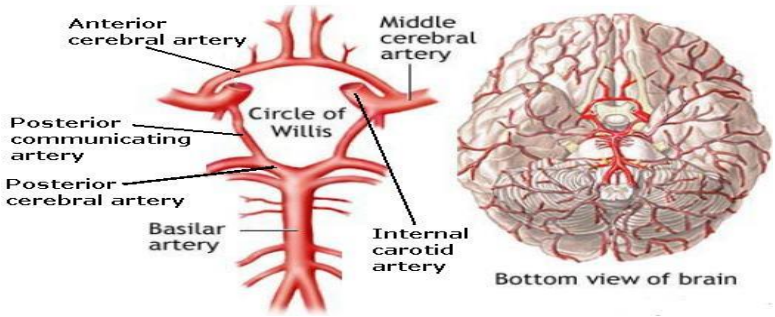

Figure 2: Circle of Willis (Baldwin *et al* , 2014, chapter .10)

Yamakami *et al.* (1987, p. 303) found that volume expansion and haemodilution, with no subsequent change in blood pressure, initially decreased cerebral blood flow, although with no change from the 3rd week post-SAH. It was in the patients in whom no change in cerebral blood flow occurred that symptomatic vasospasm was absent . However, the causal direction of this association was not obvious from the study and the sample was small, including only 35 patients. This means that it is difficult to be sure that the results are not attributable to chance (Schulz & Grimes, 2005, p. 1348). Another study by Origitano *et al.* (1990, p. 729) showed quite the opposite, with volume expansion and haemodilution leading to increased cerebral blood flow, remaining so at the 3rd week post-SAH. The reason for this difference is unclear, although the complexities of treatment in the ICU could mean that there were other differences in treatment which have not been described in detail in the papers. In the study by Origitano *et al.* (1990, p. 729) angiographic vasospasm was measured and found to have no correlation with cerebral blood flow. Another study by Lennihan *et al.* (2000, p. 383) randomised 82 patients to receive hypervolaemic or normovolaemic fluid therapy after SAH, until the 14th day. Their results showed no significant difference between groups, with 20% of patients. This was most likely due to the observation that there was no significant difference in blood volume between the groups from the third day onwards, and therefore no difference in the minimum cerebral blood flow.

Touho *et al.* (1992, p. 671) focused on the hypertension component of triple H therapy and found that infusion of dopamine, to increase blood pressure through cardiac output, was associated with improved cerebral blood flow. However, in spite of this, all patients progressed to angiographic vasospasm, with 8 of 20 also developing clinical vasospasm.

There are fewer studies which have evaluated the full triple H approach, rather than individual components. One RCT that evaluated a true triple H approach was conducted by Egge *et al.* (2001, p. 593) on 32 patients, comparing hypervolemic hypertensive hemodilution fluid therapy to normovolemic fluid therapy. The study found no difference in the incidence of delayed vasospasm, either clinically or based on TCD measurement. There were also no differences noted on SPECT analysis at 12 days post-SAH. The prospective, randomised nature of the trial makes the inclusion of selection bias less likely (Barton, 2000, p. 255; Glasser, 2008, p. 23). However, no indication was provided as to which data sets were tested with parametric and non-parametric tests. The small sample size is likely to have invalidated many of the underlying assumptions of parametric testing, such as approximation of data to a normal distribution (Daly, 2000, p. 207), therefore calling into question the validity of the results.

Another study examining all elements of triple H therapy was described by Muench *et al.* (2007, p. 1844). They examined each component in turn in animal models and human patients and determined that neither hypertension nor hypervolaemia had any significant effect in animal models. However, in human patients, inducing hypertension to a mean arterial pressure of 140 mmHg was associated with an increase in blood flow and oxygenation.In contrast, induction of hypervolaemia or haemodilution had no impact on oxygenation. The authors therefore concluded that there was no benefit to use of triple H therapy over induced hypertension alone.

One of the most important conclusions drawn by Origitano *et al.* (1990, p. 739) is that triple H therapy is a safe modality for prevention of SAH, based on the observation that all patients who received this intervention remaining stable or improving.However, another study by Papavasiliou *et al.* (2001, p. 138) contradicted this, with 2 patients of a sample of 123 dying of complications attributed to triple H therapy. However, Dorsch (2002, p. 129) notes that it is often difficult in practice to maintain a desired blood pressure. Furthermore , large volumes of fluid are also argued to increase the potential for electrolyte disturbance, which can lead

to pulmonary oedema and other complications. Therefore, although widely used, this is still not necessarily sufficient alone for prevention of vasospasm.

4.2 Calcium Channel Blockers

Given the critical role of cell-signalling pathways in the pathophysiology of cerebral vasospasm, calcium channels may prove a key intervention in its treatment (Zubkov *et al.,* 2003, p. 49). Administration of calcium channel blockers was shown by Abe *et al.* (1994, p. 99) to lead to a rapid decrease in arterial blood pressure in patients undergoing surgical intervention for their SAH. This was also associated with an increase in local cerebral blood flow, although only for nicardipine and not for diltiazem. It was shown to be associated with no change in oxygen saturation.

Feigin *et al.* (1998, p. 876) performed a meta-analysis of 10 RCTs using nicardipine or nimodipine, including a total of 2756 patients. They concluded that the relative risk reduction associated with prophylactic use of calcium channel blockers was 16% (95% confidence interval (CI) 6-27%), although this varied depending on whether ischemic neurological deficit or cerebral infarction detected on CT scan was used as the outcome measure. The risk reduction associated with calcium channel blockers for these outcomes was 33% and 20% respectively. The researchers also concluded that the number needed to treat to generate a favourable outcome was 19, although this was reduced to 13 when considering nimodipine alone.However, nicardipine was associated with a statistically significant risk reduction for angiographic vasospasm, where nimodipine was not.

There are also a number of other relevant studies not included in this review, most of which have been conducted since this systematic review was published.One study by Haley *et al.* (1993, p. 537) was most likely not included as it examined IV administration of calcium-channel blockers for 14 days prophylactically after SAH, specifically nicardipine. The authors found that compared to placebo, there was initially a significantly lower incidence of symptomatic cerebral vasospasm, with and incidence of 32% vs. 46% ($p < .001$). However, this was no longer evident at 3 months. However, in spite of the randomised, double-blind nature of this trial, there were differences between groups which could have confounded this result , but which were not adjusted for in the analysis (Matthews & Farewell, 2007, p. 47). This includes the lower rates of antihypertensive medication use and triple H therapy use in the intervention group. The effects of this difference are not clear, as lowering blood pressure could have increased the risk of vasospasm in the placebo group (Lee *et al.,* 2006, p. 69), while receiving triple H therapy would be expected to have lowered their risk, based on the discussions earlier in the review. Overall, this study found that 55% of patients receiving IV nicardipine had a favourable outcome, as measured using the Glasgow Outcome Scale (GOS), with a mortality of 17%, neither of which wassignificantly different from the placebo group.

Kronvall *et al.* (2009, p. 58) reported on an RCT in which nimodipine was administered to 106 patients, either orally or via IV infusion. The authors found no difference between administration methods with regard to delayed ischaemic neurological deficits, with an incidence of 28% in those receiving oral medication and 30% in those receiving it via IV. The authors also found no difference in cerebral blood flow methods between groups. 50% of those in the oral treatment group and 45% in the IV treatment group met the definition of TCD spasm, according to Frontera *et al.* (2009, p. 1963), with flow velocity of more than 120cm/s. There were also no differences in clinical outcome, as measured by the GOS.

A total of 74.8% of a consecutive sample of 123 patients treated with diltiazem were reported by Papavasiliou *et al.* (2001, p. 138) to have experienced favourable outcomes, as measured according to the GOS. The researchers also found that 24 of these patients developed delayed ischaemic neurological deficit, seven of which subsequently experienced poor functional outcomes or death as a result. Although the authors compared this to contemporary series of patients receiving other interventions and concluded diltiazem to produce favourable outcomes, there were no controls included for direct comparison.

Kronvall *et al.* (2009, p. 58) found no differences in the clinical safety of offering patients oral or IV calcium channel blockers. It is likely that patients who have suffered an SAH could have neurological impairment which would mandate the use of IV medications rather than oral forms. The evidence overall seems to support the use of calcium channel blockers in preventing SAH, although most of these studies were observational, and there is a need for RCTs in this area.

An important consideration in the potential use of calcium channel blockers is that there was some suggestion by Abe *et al.* (1994, p. 99) that their efficacy could vary according to the patient's pre-intervention neurological status. Although this was based on only a relatively small sample of 26 patients, and did not evaluate vasospasm as an outcome, it showed that local cerebral blood flow

change was correlated with pre-intervention neurological status.

4.2.1 Intra-arterial Infusion

There have been a limited number of studies examining the effects of intra-arterial infusion of calcium channel blockers during endovascular procedures in preventing delayed cerebral vasospasm. Saunders and Marshall (1986, p. 155) found that while no adverse clinical effects were noted, diltiazem was not associated with any significant reduction in vasospasm. However, there have still been not RCTs in this area.

4.2.2 Prolonged-Release Implants

Kasuya *et al.* (2002, p. 1011) sought to investigate whether prolonged-release nicardipine implants, already shown to be effective in dogs, would be efficacious and safe in human patients. Although the study showed that there was no angiographic vasospasm in any sites near the implant placement sites, one patient did exhibit clinical symptoms, with delayed neurological deficits. This study included only a small sample, with 20 patients initially identified. Furthermore, only 10 implants were actually placed, based on patient factors during clipping of the aneurysm. Although this was not an RCT, it could still lead to the same issues with generalisation as would be generated through absence of an intention-to-treat analysis (Abraha & Montedori, 2010, p. 1). That is, patients were chosen to receive the treatment or not based on certain characteristics. Therefore the sample which received the intervention may not be representative of the whole population, but share a set of characteristics which may make this particular intervention more likely to be successful. Therefore the results could be less likely to be generalizable to the entire population of patients with SAH (Hinton, 2014, p. 42). The study suggested that the intervention was safe, with no adverse clinical events noted.

These authors repeated the trial in a much larger sample of 97 patients (Kasuya *et al.*, 2005, p. 895). This study further supported the argument that use of a modified-release nicardipine was associated with a reduced risk of delayed ischemic events, seen in 6% of those receiving the intervention and 11% in those without. However, there was no statistical analysis regarding the significance of these findings, which means that the hypothesis has not been truly tested (Riegelman, 2005, p. 37). Also, patients receiving the intervention were again selected, rather than being randomised. This means that the paper most likely suffers from the same issues as the authors' earlier study, in spite of the larger sample size (Kasuya *et al.*, 2002, p. 1011).

4.3 Erythropoietin

Erythropoietin (EPO) is a hormone which regulates homeostasis of blood within the body, via stimulation of red cell production. Endogenous EPO levels change in response to O_2tension, rising in response to low levels of oxygen within the blood. This then stimulates differentiation and proliferation of erythrocytes within the bone marrow, increasing haemoglobin levels and therefore oxygen-carrying capacity (Elliott *et al.*, 2008, p. 1573). Erythropoiesis-stimulating agents, analogues of EPO, have been demonstrated to have a role in treatment of anaemia, particularly where low haemoglobin levels are attributable to lack of endogenous EPO production, such as in chronic kidney disease (Phrommintikul *et al.*, 2007, p. 381). However, EPO has also been demonstrated under stress conditions to improve the survival of neurones in animal models (Celik *et al.*, 2002, p. 2258; Kumral *et al.*, 2003, p. 224; Kertmen *et al.*, 2014, p. 951).

The role of EPO in protection against delayed vasospasm has also been investigated. An experimental study by Chen *et al.* (2009) identified that EPO could activate JAK2/STAT3 pathways, reducing the rate of apoptosis of endothelial cells. Although based on an animal model, this suggests that EPO could have a potential role in protection against post-SAH delayed vasospasm. This has been supported by a further study in a rabbit model by Kertmen *et al.* (2014, p. 951), which demonstrated EPO attenuated cerebral vasospasm. However, a small UK-based RCT by Tseng *et al.* (2009, p. 171) found no difference in the incidence of delayed vasospasm in patients receiving EPO 72 hours post-haemorrhage when compared to placebo. As this was a double-blind trial with a well-defined randomisation process, the results would be expected to have high levels of reliability and validity (Jadad *et al.*, 1996, p. 1; Barton, 2000, p. 255).

The study by Tseng *et al.* (2009, p. 171) did, however, find that administration of EPO was associated with lower severity and shorter duration of autoregulation dysfunction. They also observed a more favourable outcome at discharge, as measured by Glasgow Coma Scale (G CS) score (Table1) and National Institutes of Health Stroke Scale, when compared to placebo. Their trial did not specifically explore the mechanism underlying these results, although other studies have shown that EPO increases brain tissue oxygen tension (Helbok *et al.*, 2012, p. 1) and cause vasodilation in spastic arteries (Santhanam *et al.*, 2005, p. 2731).An experimental study by Santhanam *et al.* (2005, p. 2731) suggested that EPO could exert a protective effect through

phosphorylation of protein kinase B (Akt) and endothelial nitrous oxide synthase (eNOS), leading to vasodilation. However, the results of the study by Tseng *et al.* (2009, p. 171) are not conclusive, with only a relatively small sample size (Schulz & Grimes, 2005, p. 1348);. Moreover, another similar sized study by Springborg *et al.* (2007, p. 1089) found no significant improvement associated with EPO administration, despite following an almost identical protocol.

Best motor response		Best verbal response	
6	Obeying commands	**5**	Oriented (time, place, person)
5	Localizing to pain	**4**	Confused conversation
4	Withdrawing to pain	**3**	Inappropriate speech
3	Flexor response to pain	**2**	Incomprehensible sounds
2	Extensor response to pain	**1**	None
1	No response to pain		

Table 2: Glasgow Coma Scale (GCS) Score Baldwin *et al* , 2014, chapter.20)

More recent studies have explored the potential for EPO analogues, which act to stimulate EPO receptors. Kertmen *et al.* (2014, p. 951) noted better histopathological results in a small sample of rabbits. However, there are yet to be clinical trials to evaluate these novel treatments.

4.4 Tirilazad Mesylate

Tirilazad mesylate is a corticosteroid that has been shown to have neuroprotective properties (Castanares-Zapatero & Hantson, 2011, p. 2). As steroids have anti-inflammatory properties, it would be expected that this would aid prevention of vasospasm, given the underlying inflammatory mechanisms. In addition, tirilazad has antioxidant properties that block the effect of free radicals, which induce peroxidation of membrane lipids and promote vasospasm (Castanares-Zapatero & Hantson, 2011, p. 2).

Efficacy has been demonstrated in animal models of stroke (Kanamaru *et al.*, 1990, p. 29). For example, in an RCT using monkeys, with control group given normal saline placebo, less angiographic vasospasm was observed in the treatment group, although this was limited to certain areas, specifically the middle cerebral artery and anterior cerebral artery. This result held across different dosages, although the lowest dosage used, 0.3 mg/kg, was also associated with reduced vasospasm in the extradural internal carotid artery; however thisdifference was not significant. The benefit of the animal model study was that it allowed for microscopic examination of the brain tissue. This demonstrated that luminal convolutions and endothelial cell morphological changes were both still present in the treatment group, although were subjectively deemed to be less prominent in this group.

One of the largest studies of any treatment to prevent delayed cerebral vasospasm was that of Kassell *et al.* (1996, p. 221), a multi-centre study involving 1023 patients. The study found that treatment with tirilazad was associated with a reduced incidence of symptomatic vasospasm, although the effect did not reach statistical significance, which means that it is not possible to be certain that the results could not be attributable to chance (Schulz & Grimes, 2005, p. 1348). This could potentially be attributable to the co-administration of nimodipine in these patients. As already discussed earlier in the work, there is some evidence for calcium channel blockers, including nimodipine, in reducing incidence of delayed cerebral vasospasm (Kronvall *et al.*, 2009, p. 58). Therefore it could be that tirilazad produces no additional benefit, but could potentially be useful if administered alone. However, when examining the significance calculations, the significance achieved by the test was $p = 0.048$, which is significant at the 95% confidence level. Therefore it would be argued that there still is some evidence of possible statistical significance here. This difference was also found only in those who received higher doses of 6mg/kg, with no effect at lower doses when compared to a citrate placebo. The authors also noted that the effect was more pronounced in male than female patients, although no further explanation for this observation was offered. However, the study did find that there was a statistically significant reduction in mortality in the group who received the higher dose of tiralazad ($p = .01$) and also showed better recovery, as measured by the GOS.

A further multi-centre study in the U.S. was described by Haley *et al.* (1997, p. 467), although the results in this study were less promising than those in the study by of Kassell *et al.* (1996, p. 221). Here,

there was also no significant difference between the rates of symptomatic vasospasm seen in patients receiving tirilazad or placebo in the first 14 days after SAH, regardless of dose. They also found no difference in severity of these episodes. However, here again, all patients also received nimodipine. A number of patients in each group also received triple H therapy, although rates were similar across groups. Unlike the study by Kassell *et al.* (1996, p. 221), this study found no difference in rates of mortality, or clinical outcome as measured by the GOS between groups at 3 months after SAH. However, when stratifying according to gender and initial GOS score, there was some evidence of a reduced mortality in men with higher grade neurological status on admission, with mortality reducing from 33% to 5% at doses of 6mg/kg (p = .03).

Lanzino *et al.* (1999, p. 1011) also reported on a double-blind, multicentre RCT, but focused on treating female patients with tirilazad at a higher dose of 15 mg/kg/day. They found that there was a reduced rate of cerebral vasospasm within the first 14 days after SAH in those given the intervention. However, there was no difference in mortality or clinical outcome, as measured by the GOS. There was also one important difference between the two groups, which was that there was a significantly greater use of triple H therapy in the treatment group, which could be a confounding factor (Matthews & Farewell, 2007, p. 47), based the possible effects already discussed earlier in this paper.

Lanzino and Kassell (1999, p. 1018) further expanded on the study by Lanzino *et al.* (1999, p. 1011) in the U.S., with similar results to those observed by Haley *et al.* (1997, p. 469). Their study showed that in females with higher neurological functioning on admission, high dose tirilazad of 15 mg/kg had lower mortality, reducing from 43.4% to 24.6% (p = .016). This therefore shows a similar trend to that seen in male patients (Haley *et al.*, 1997, p. 469). Again, this study showed no significant difference in the rate of symptomatic vasospam between groups, or in the severity. However, for those with lower grade neurology, it was noted that there were more favourable outcomes in the placebo group, with 76.7% mortality compared to 83.3% in the treatment group (p = .04).

It was noted by authors that tirilazad is well-tolerated by patients (Kassell *et al.*, 1996, p. 221; Haley *et al.*, 1997, p. 467). However, some of the results have shown that this may depend on the initial neurology of the patient, with some evidence of greater risk of mortality in those with poorer neurological status who then were treated with tirilazad (Lanzino & Kassell, 1999, p. 1018).

When examining the evidence from these studies overall, shown in Figure 3, it can be seen that there is good evidence for the use of tirilazad in preventing vasospasm, with none of the studies reporting concerning adverse reactions to its use. The odds ratios calculated are shown in Appendix 1.

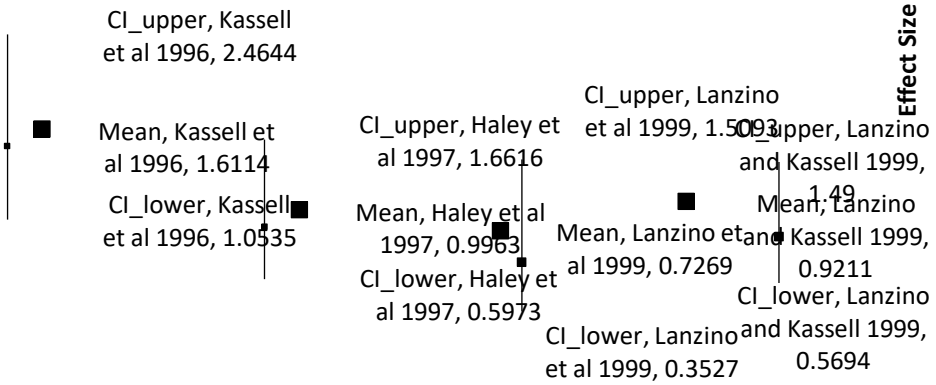

Figure 3: The odds ratios of studies which have examined the effect of tirilazad in prevention of delayed cerebral vasospasm

4.5 Statins

Statins inhibit an enzyme which is involved in cholesterol synthesis and also exert anti-inflammatory effects, stabilising atheromatous plaques and preventing adhesion to the endothelium (Weitz-Schmidt, 2002, p. 482). Animal studies which have sought to understand how statins may prevent vasospasm have shown that they also reduce the level of chemoattractant production and immune cell infiltration (Aoki *et al.*, 2008, p. 1276), while increasing vessel diameter (McGirt *et al.*, 2006, p. 945). However, subsequent studies in humans have shown there to be no significant effect of statins on inflammatory markers (Vergouwen *et al.*, 2009, p.

1444). The main mechanism by which they are thought to reduce vasospasm is through increasing nitrous oxide synthesis, which induces vasodilation and improves blood flow (Aoki *et al.*, 2008, p. 1276). One retrospective study suggested that those treated with statins before developing an SAH are at significantly less risk of developing delayed cerebral ischaemia (McGirt *et al.*, 2006, p. 671). This could be due to their effects on medial thickness and reduced size of aneurysm (Aoki *et al.*, 2008, p. 1276). However, another study by Kern *et al.* (2009, p. 527) contradicted these findings.

Lynch *et al.* (2005, p. 2024) found that clinical vasospasm was significantly reduced in those who received simvastatin for 14 days after SAH ($p < .05$), although this was based on only a very small sample size. They also noted that velocity was significantly lower in the treatment group ($p < .01$), suggesting that the reduced incidence of vasospasm could be associated with the changes of blood flow induced by the statins.

Similar results have also been shown in subsequent studies. For example, Tseng *et al.* (2005, p. 1627) found that incidence and severity of vasospasm was reduced, along with the duration of vasospasm. In this study, this also correlated to a reduced mortality. However, not all studies agree. Vergouwen *et al.* (2009, p. 1444) found no significant difference associated with treatment, although this was using simvastatin rather than pravastatin. There were also a significant number of patients excluded from the study, which could hint at selection bias (Barton, 2000, p. 255; Glasser, 2008, p. 23). Kramer *et al.* (2008, p. 422) also found statins had no effect on either symptomatic or angiographic vasospasm. However as this was a retrospective chart review, in which a significant number of charts were excluded, there is also a potential for selection bias (Barton, 2000, p. 255; Glasser, 2008, p. 23). Chou *et al.* (2008, p. 2891) also found significant differences in angiographically-confirmed vasospasm, although actually found it to be increased in the statin treatment group; however this was again only a small study. The largest study currently available, however, is the simvastatin in aneurysmal subarachnoid haemorrhage (STASH) study, which found no difference in rates of delayed ischaemia, although this study did only use doses of 40 mg/day rather than 80 mg/day.

Taking this evidence overall, figure 4 shows that there is again good evidence that statins reduce the risk of cerebral vasospasm in patients with SAH. However, one of the main concerns regarding the use of statins is that they may be associated with serious side effects, including myositis and hepatitis. Although these have not been noted to occur in patients in most of the studies described here (Lynch *et al.*, 2005, p. 2024), there were a number of patients in the STASH study who had statin-related liver dysfunction (Kirkpatrick *et al.*, 2014, p. 671). Therefore patients who receive these may need to be carefully selected.

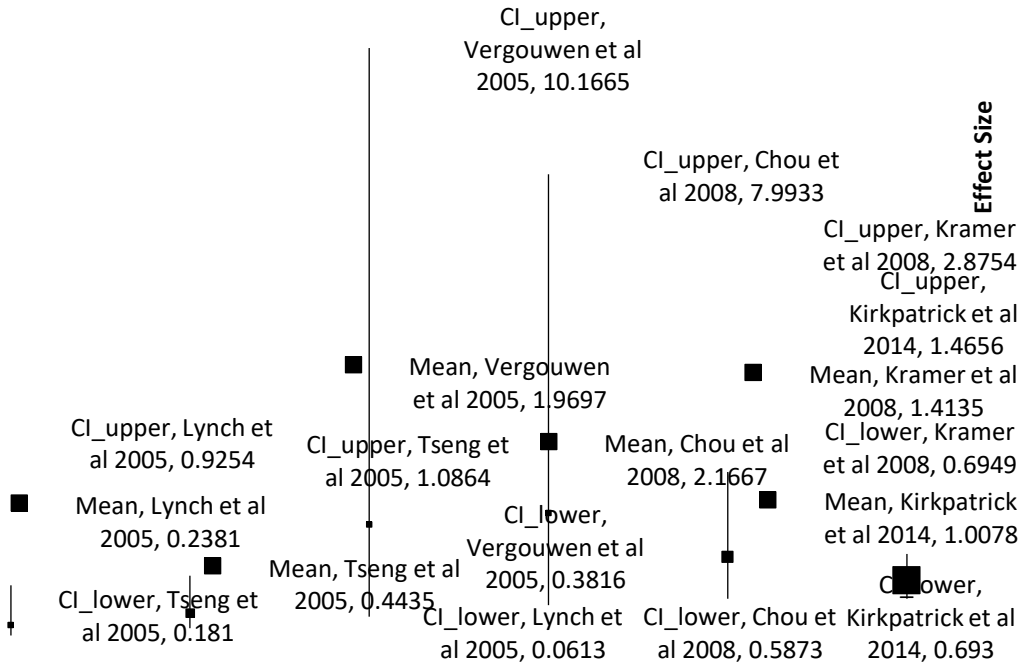

Figure 4: The odds ratios of studies which have examined the effect of statins in prevention of delayed cerebral vasospasm

4.6 Magnesium Sulphate

Magnesium sulphate blocks voltage-gated calcium channels (Castanares-Zapatero & Hantson, 2011, p. 3) and animal studies have shown that magnesium exerts a neuroprotective effect (Marinov *et al.*, 1996, p. 117).

Veyna *et al.* (2002, p. 510) examined the effect of treatment with magnesium sulphate for 10 days after SAH and found that this had no noticeable effect on the incidence of angiographic vasospasm. They also found it to have no effect on cerebral perfusion, or on clinical outcomes, as measured by the GOS. Wong *et al.* (2006, p. 142) also found there to be no significance, in spite of there being a reduction in incidence of vasospasm from 43% to 23%. This could be associated with the small sample sizes which were used (Daly, 2000, p. 207), as other small studies (Chia *et al.*, 2002, p. 279), along with a larger study by van den Bergh *et al.* (2002, p. 1014) have shown magnesium to be effective in reducing the risk of clinical vasospasm. Also, when examining the results of the studies overall, as shown in Figure 5, this shows that there is relatively good evidence for the effect of magnesium. It has also been noted that magnesium sulphate is safe, with no adverse events noted from the studies reviewed (Veyna *et al.*,2002).

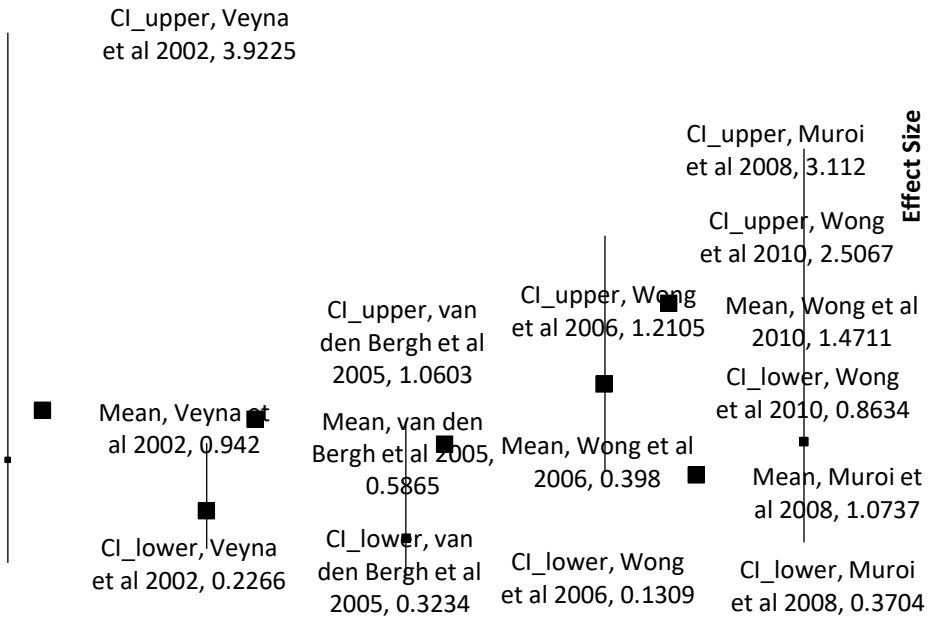

Figure 5: The odds ratios of studies which have examined the effect of magnesium in prevention of delayed cerebral vasospasm

4.7 Endothelin Receptor Antagonists

Endothelin is a powerful vasoconstrictor which acts on smooth muscle cells, and has been noted to increase in response to SAH (Zimmerman & Seifert, 1998, p. 863). Therefore agents which block this would be expected to reduce vasoconstriction post-SAH. Agents which have been used include clazosentan.

Shaw *et al.* (2000, p. 992) claimed to have found a lower incidence of cerebral vasospasm in their multicentre RCT. However, when examining the confidence intervals, this indicates that the reduction in incidence is not significant (Fletcher & Fletcher, 2005, p. 174). The results in the study by Vajkoczy *et al.* (2005, p. 9) were more convincing, and showed that the incidence and severity of vasospasm was reduced in those treated with endothelin receptor antagonists. However, this was only a very small study, which may lead to problems with generalisation of results (Schulz & Grimes, 2005, p. 1348). However, the results are also supported by a much larger study by Macdonald *et al.* (2008, p. 3015), which showed that incidence of vasospasm reduced from 66% to 23% in those who received the highest dose of clazosentan, one of the major endothelin receptor antagonists available. However, when examining the data together, as in Figure 6, it would seem that there is less evidence than for some of the other interventions discussed so far. It is also important to note that studies have shown that clazosentan may carry considerable risk, including pulmonary complications, hypotension and anaemia (Macdonald *et al.*, 2008).

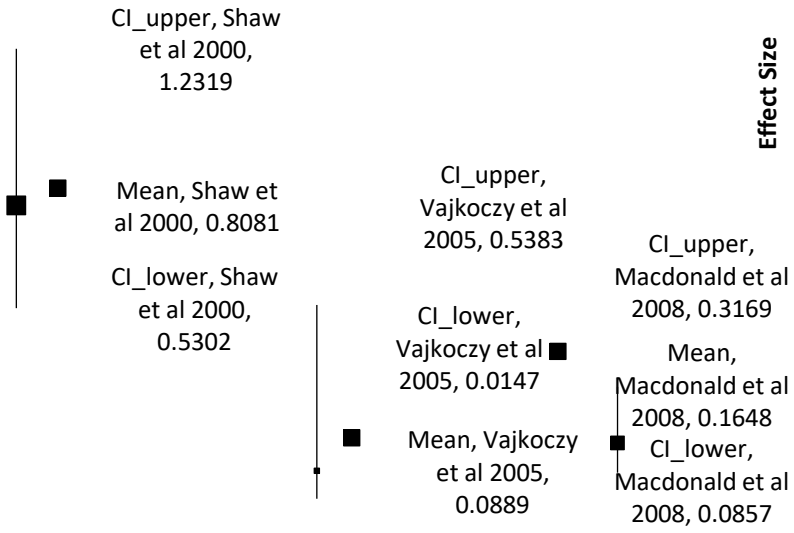

Figure 6: The odds ratios of studies which have examined the effect of endothelin receptor antagonists in prevention of delayed cerebral vasospasm

4.8 Fasudil

Fasudil inhibits the enzyme rho-kinase, which usually acts to induce smooth muscle contraction, thereby preventing vessels from constricting (Castanares-Zapatero & Hantson, 2011, p. 4).There have been fewer studies examining fasudil than many of the other interventions discussed in this review. Shibuya *et al.* (1992, p. 571) found it significantly reduced vasospasm when compared to a placebo, regardless of whether this was measured angiographically, on CT or clinically. It would also appear from the results that vasospasm was less severe, although this was not formally statistically tested. Zhao *et al.* (2006, p. 421) noted similar results, although the lower incidence of vasospasm was not statistically tested and this was a much smaller sample. When administered as intra-arterial therapy in conjunction with removal of clots and urokinase injectionit has been shown to generate a significant reduction in vasospasm, along with better outcomes (Hamada *et al.*, 2003), although this was based on only a small study. It has been shown that there is little risk associated with providing patients with fasudil, with no adverse events noted in the studies (Shibuya *et al.*, 1992, p. 571); however, overall there is little evidence at present that this offers such promise as other preventive therapies discussed , as show in Figure7.

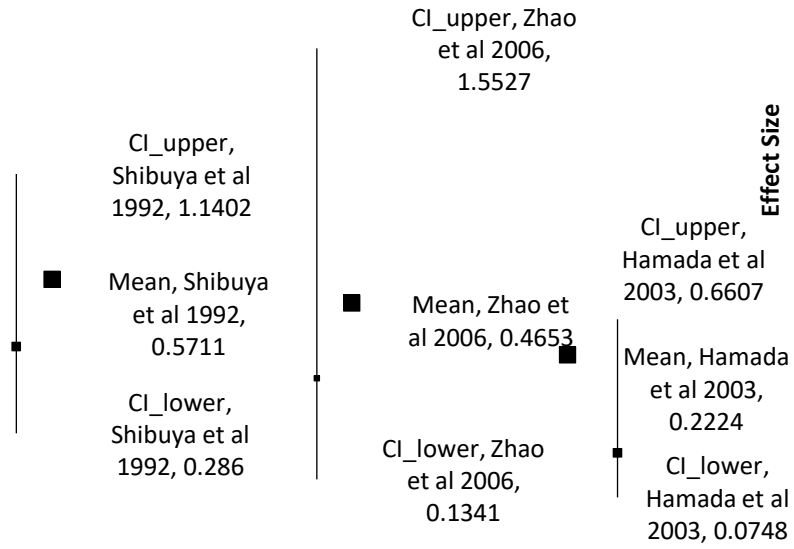

Figure 7: The odds ratios of studies which have examined the effect of fasudil in prevention of delayed cerebral vasospasm

4.9 Antiplatelet Therapy

Antiplatelet therapy has been proposed as a possible intervention to reduce the risk of vasospasm due to the role of platelet aggregation and thromboxane in this process. However, a systematic review by Dorhout *et al.* (2007, p. 1) demonstrated that there was little evidence for the use of antiplatelet therapy in practice. The study did note that one antiplatelet, ticlopidine, was associated with slightly improved clinical outcome, although did not reduce the risk of vasospasm. This would be considered strong evidence, as the review was taken from the Cochrane Database, which has one of the strictest protocols available for conducting this type of review (Saimbert *et al.*, 2012, p. 109).

4.10 Albumin

Albumin is believed to have a neuroprotective role, as demonstrated in other forms of brain injury. One proposed mechanism for this is scavenging of free radicals and other substances which may mediate endothelial dysfunction (Castanares-Zapatero & Hantson, 2011, p. 4).Patients who received albumin were found by Suarez *et al.* (2004, p. 585) to have lower rates of vasospasm than those who had not received albumin. As this study was not an RCT, there is therefore some potential for bias, as there were underlying characteristics shared within each group which had resulted in them being allocated that treatment (Barton, 2000, p. 255; Glasser, 2008, p. 23). The study also found that these patients were more likely to have a good clinical outcome at 3 months post-SAH. However, it is possible that this could be associated with the same underlying factors which determined treatment group of the patient, rather than reflecting the effects of the albumin.

4.11 Thrombolytics

As there is some potential that substances released from clots contribute to vasospasm, thrombolytics have also been investigated for prevention. A meta-analysis of studies performed by Amin-Hanjani *et al.* (2004, p. 334) found that across nine RCTs, there was a statistically significant reduction in the risk of delayed cerebral ischaemia, improved clinical outcomes and reduced risk of mortality. This did not seem to vary according to whether the thrombolytic used was tissue plasminogen activator or urokinase. It also was not affected by whether the intervention was applied intraoperatively or postoperatively. However, there are significant risks to some patients from being treated with thrombolytics (McDowell *et al.*, 2006, p. 1), which could still make these less suitable than alternatives already discussed here.

4.12 Enoxaparin

Wurm *et al.* (2004, p. 97) found that enoxaparin reduced the incidence of both clinical and local angiographic vasospasm when given once daily for three weeks after SAH. This was a good quality RCT, although when taken in isolation, it is difficult to evaluate the reliability of these findings.

4.13 Thromboxane Synthetase Inhibitor

Thromboxane is another substance which is associated with vasoconstriction, so reducing its effects should mediate dilation of cerebral vessels (Kassell *et al.*, 1985, p. 563).. Suzuki *et al.* (1989, p. 79) found that the incidence of vasospasm significantly lower in those who received a thromboxane synthetase inhibitor and also improved sooner. This should constitute strong evidence given it was derived from a multicentre, double-blind study, although the full results were not available from which to evaluate the integrity of conclusions drawn.

4.14 Free Radical Scavengers and Antioxidant Agents

The theory behind the use of antioxidant agents is that free radicals induce peroxidation of membrane lipids and promote vasospasm (Castanares-Zapatero & Hantson, 2011, p. 2). Therefore mopping these up, using agents such as edaravone and ebselen, could moderate vasospasm. This certainly seems to be supported in studies on rats, where it has been shown to exert a neuroprotective effect (Gul *et al.*, 2010, p. 608).Saito *et al.* (1998, p. 269) found there to be a significantly reduced incidence of ischaemic deficit in those treated with ebselen at 3 months after SAH. This should constitute strong evidence, as it was derived from a double-blind, multicentre trial (Jadad *et al.*, 1996, p. 1). However, there is yet no other evidence to support the findings.

5. Clinical Interventions

While prevention of vasospasm may be preferable, there remained some who developed vasospasm in spite of preventive measures in all studies discussed in the previous chapter. Therefore there has also been some interest in developing therapeutic interventions to reverse vasospasm, which will be discussed here.There are currently no British guidelines available on treatment of cerebral vasospasm, although at present, U.S. guidelines suggest the use of intra-arterial calcium channel blockers or transluminal balloon angioplasty as the two main treatment options (Abbruzzo *et al.*, 2012, p. 169). The main studies in this area are summarised in Table 3, although the body of work here is much smaller than for prophylaxis.

Table 3: Studies examining the effect of interventions for treating delayed cerebral vasospasm

Author	Intervention	Study Design	Sample	Main Findings
Muizelaar & Becker (1986)	Induced hypertension	Observational	43 patients	Immediate positive clinical outcome in all patients
Yamakami *et al.* (1987)	Intravascular volume expansion	Observational	35 patients	No effect on cerebral vasospasm
Touho *et al.* (1992)	Induced hypertension	Observational	20 patients	Intervention reversed cerebral vasospasm
Darby *et al.* (1994)	Induced hypertension	Observational	13 patients	Therapy improved cerebral blood flow
Mori *et al.* (1995)	Triple H therapy	Observational	98 patients	Intervention effective in reversing cerebral vasospasm
Thomas & Rosenwasser (1999)	Intrathecally administered NO donor in refractive cases of vasospasm	Case series	3 patients	All three patients had their vasospasm reversed, including clinical improvement, angiographic and TCD ultrasound review
Dorsch (2002)	Balloon angioplasty Chemical angioplasty	Review of 41 publications	< 400 patients	Immediate clinical improvement in patients: 55% in balloon angioplasty 40% chemical angioplasty
Kim *et al.* (2003)	Triple H therapy	Observational	16 patients	Intervention improved cerebral blood flow
Siironen *et al.* (2003)	Enoxaparin 40mg	Double-blind RCT	170 patients	No effect on outcome in patients who had already received nimodipine and triple H therapy
Reinert *et al.* (2004)	Nitroglycerin 14 microgrammes/kg/hr	RCT	17 patients	Nitroglycerin reduces blood pressure, but also increases cerebral blood flow; this did not increase the risk of delayed cerebral ischaemia
Hui & Lau (2005)	Intra-arterial nimodipine	Retrospective chart review	9 patients	Intervention effective at improving vasospasm
Jost *et al.* (2005)	Volume expansion	Observational	6 patients	Improved cerebral blood flow
Vajkoczy *et al.* (2005)	Clazosentan 0.4 mg/kg/hr for 12 hours, followed by 0.2 mg/kg/hr (endothelin receptor antagonist)	Patients receiving the placebo in a double-blind, multicentre RCT were subsequently given treatment if they developed vasospasm	19 patients	50% of patients who were treated had their vasospasm reversed
Agrawal *et al.* (2009)	Intraventricular sodium nitroprusside, starting at 4 mg/mL and increasing as required	Prospective observational study	20 patients	Treatment associated with improvement in blood flow velocity and neurological status when compared to those not receiving treatment
Schmidt *et al.* (2010)	Intra-arterial icardipine	Retrospective chart review	73 patients	Improvements in vessel calibre with therapy

5.1 Current Treatments

5.1.1 Triple H Therapy

In spite of being relatively commonly used, the lack of effect on cerebral blood flow when triple H therapy was initiated as a prophylactic measure has also been noted when its potential for therapeutic intervention has been explored. Muizelaar and Becker (1986, p. 317) found that treatment with phenylephrine to induce hypertension was associated with a significant increase in cerebral blood flow. However, the role of haemodilution in these patients was debatable, as three of five patients were already noted to have high haematocrits, and one was treated to induce haemodilution. The study also noted that there was a clinical effect in all five patients, although there was no evidence of objective measurement of symptoms.

The study by Yamakami *et al.* (1987, p. 303), which preliminary investigated triple H therapy as prophylaxis, also noted that volume expansion did not subsequently reverse symptomatic vasospasm. However, as noted earlier in the review, there may be a substantial number of patients who develop angiographic vasospasm, or vasospasm measurable with TCD, who do not experience symptomatic vasospasm. This study, therefore, does not allow conclusions to be drawn on the effect of volume expansion on these patients.

Touho *et al.* (1992, p. 671) suggested that induced hypertension could reverse the neurological deficits associated with delayed vasospasm. However, it was not made clear in their methodology as to how this was achieved, as it would appear that all participants had received the hypertensive medications as a continuous infusion. Yet some participants still went on to develop clinical vasospasm.

A small study by Darby *et al.* (1994, p. 857) explored the impact of increasing blood pressure via administration of dopamine. They found that this increased local cerebral blood flow in more than 90% of the areas which did not contain an infarct but had previously been ischaemic. In the areas which had never been ischaemic, administration of dopamine decreased cerebral blood flow in one third. However, potentially the most important finding of this study was that the change in cerebral blood flow observed was correlated with the resting flow prior to administration of the dopamine, and was unrelated to blood pressure. These results indicate that administration of dopamine may have unpredictable effects, possibly due to other underlying moderating factors. It also indicates that dopamine may be much less important in determining cerebral blood flow changes than the patient's resting cerebral blood flow rate. This is difficult to disprove as there were no controls included in this study (Romesburg, 2009, p. 110).

Mori *et al.* (1995, p. 1620) examined the effect of hypervolemic hemodilution therapy in patients undergoing surgery for SAH. They found this effectively brought patients back from hypovolaemia to normo- or hypervolaemia, with associated reduction in haematocrit. It was also noted that this therapy did lead to an increase in cerebral blood flow in both hemispheres, including that on which surgery had been performed and the aneurysm had occurred. Although this study had a moderate sample size, with 51 patients, the researchers did not assess whether the therapy resulted in any clinical effect on the aneurysm, either through angiographic assessment of the vasospasm or via measurement of clinical outcomes.

A study by Kim *et al.* (2003, p. 1044), utilising xenon CT blood flow monitoring, suggested that it was actually an increase in cardiac output, induced by phenylephrine or dobutamine, which was associated with improved cerebral blood flow, independent of blood pressure change. Ekelund *et al.* (2002, p. 703) also found hypervolaemic haemodilution to be associated with no improvement in cerebral blood flow, while isovolaemic haemodilution was. Importantly though, this was associated with a reduced oxygen delivery rate, so would still be expected to be of no value in prevention of delayed cerebral ischaemia. However, both of these studies were again based on only very small samples, of 16 patients and 8 patients respectively.

One of the most controlled experimental studies described in the literature was conducted by Jost *et al.* (2005, p. 25). The researchers used positron emission tomography (PET) scanning to measure cerebral blood flow in patients prospectively recruited after SAH, but prior to developing vasospasm.The prospective nature of the study should make introduction of bias less likely, as the clinical course taken by patients would not have been known prior to introducing triple H therapy (Barton, 2000, p. 255). It also allowed for patients to be carefully maintained as euvolemic prior to introduction of the hypervolemic or normovolemic control therapy. Therefore the effects on cerebral blood flow should have been exclusively attributable to the therapy used, in the absence of any other differences in treatments during the study (Meinert, 2012, p. 11).

The researchers found that hypervolemic therapy was associated with a substantial increase in blood flow, which was sustained for at least 3 hours post-infusion. They found that this was not associated with an increase in blood pressure or cardiac output. One of the major drawbacks of this study was that it involved only six patients. Therefore any form of statistical testing would have only very low power, making it difficult to derive any reasonable conclusions on the association between treatment and outcomes, in spite of how precise the remainder of the methodology may have been (Hulley *et al.*, 2007, p. 141; Johnson *et al.*, 2007, p. 186).
Overall, it would seem that there is relatively little evidence to support the use of triple H therapy in reversing cerebral vasospasm once it has started.

5.1.2 Transluminal Balloon Angioplasty

First described in 1984, transluminal balloon angioplasty describes a procedure in which a balloon is manoeuvred into the spastic vessel and inflated, to increase the size of the lumen (Dorsch, 2002, p. 130). This contrasts with the use of chemical angioplasty, in which angiography catheter used to administer vasodilator. Balloon angiography is suggested by Dorsch (2002, p. 130) to be more effective, based on a review of unpublished data that compared the two; this showed immediate clinical improvement in 55% of patients undergoing balloon angioplasty and 40% in those undergoing chemical angioplasty. This was based on a large sample of almost 400 patients, but it is difficult to determine the review's credibility, as no methodology or published data is presented – only for proximal arteries as risk of rupturing artery – this can be reduced by intubating and paralyzing, but this carries its own risks (Varma *et al.*, 2007, p. 75). Muizelaar and Madden (2001, p. 185) highlight that this technique still leaves substantial numbers with neurological deficit.Furhtermor , this approach requires specialised team and equipment, which may make access difficult for some patients (Dorsch, 2002, p. 130).

5.1.3 Calcium Channel Blockers

It would seem that there is some benefit to oral administration of calcium channel blockers, although they seem to exert effect via neuroprotective mechanisms rather than vasodilation (Zornow & Prough, 1996, p. 107), which prevents and limits extension of ischaemia (Castanares-Zapatero & Hantson, 2011, p. 2). This may then reduce mortality. One study described by Karinen *et al.* (1999, p. 780) suggested that patients treated with nimodipine lived an average of 3.46 years longer than those who received placebo. Studies have also shown that they are safe and cost-effective (Karinen *et al.*, 1999, p. 780; Castanares-Zapatero & Hantson, 2011, p. 2). However, these studies have been based in the U.S., so cost-effectiveness may be influenced by local factors, such as the structure and funding of the health care system and cost of medications (Welte *et al.*, 2004, p. 857).

While Saunders and Marshall (1986, p. 155) found diltiazem to be of little use in prevention of vasospasm, the evidence on treatment of symptoms is more mixed. One of the first studies examining the use of intra-arterial calcium channel blockers was published by Hui and Lau (2005, p. 1030). The authors found that administering nimodipine was associated with an increased vessel diameter of two thirds in patients treated for vasospasm. This was not associated with any change in blood pressure, which should indicate that blood flow to the surrounding tissue improved as a result (Lee *et al.*, 2006, p. 69; Muench *et al.*, 2007, p. 1844), although this was not specifically measured, as the study was based on retrospective review of case notes. The main disadvantage to this approach is that the small sample of 9 patients could therefore have had specific characteristics which influenced outcome (Barton, 2000, p. 255). Therefore the results of this study alone may not be generalizable, and they have not yet been reproduced in larger studies.

Schmidt *et al.* (2010, p. 895) administered nicardipine to patients with symptomatic vasospasm via intra-arterial infusion, with or without the addition of a second agent, milrinone, an inotrope which increases contractility of cardiac smooth muscle and is more commonly used to treat heart failure (Cuffe *et al.*, 2002, p. 1541). Their results demonstrated that more than 90% of the 73 patients showed improved vessel patency after treatment, regardless of which of the two medication combinations was administered, although the degree of improvement was less clear. There was also little information provided as to whether this correlated with clinical outcomes. The study also found that blood pressure decreased by a mean of 13% during treatment, despite increased doses of hypertensive medications such as phenylephrine, norepinephrine and vasopressin, which contrasts with the findings of Hui and Lau (2005, p. 1030). As discussed in relation to triple H therapy above, it is desirable to maintain these patients with a high mean arterial pressure(Lee *et al.*, 2006, p. 69; Muench *et al.*, 2007, p. 1844). However, the patients included in the sample had already failed to improve with triple H therapy, which could indicate they were more at risk of the effects of impaired autoregulation of blood pressure.

This could also be associated with this calcium channel blocker specifically, rather than being a class effect (Soares & Carneiro, 2002, p. 1031).
This treatment approach seems to be relatively safe. Mortality in the study by Schmidt *et al.* (2010, p. 895) was reported as 11%, although there was no comparison available for those receiving other therapies. Overall, however, it would seem that this treatment approach were safe, with only one patient experiencing an adverse event, with increased troponin T, indicating cardiac smooth muscle damage. There were also no adverse clinical effects reported by other similar studies (Saunders & Marshall, 1986, p. 155; Hui & Lau, 2005, p. 1030).
Taken overall, the evidence does seem to support the use of calcium channel blockers in reversing cerebral vasospasm once it has begun. However, there may need to be more work done on understanding how these effects are produced, to better understand whether treatment approaches can be manipulated to produce even better results.

5.2 Treatments in Development
As with preventive measures, there are a number of other treatment options that have been explored, which are summarised here.

5.2.1 Endothelin Receptor Antagonists
With endothelin receptor antagonists, most of the studies have focused on prevention of vasospasm. However, the study by Vajkoczy *et al.* (2005, p. 9) consisted of two parts, with the second part involving treatment to those patients who initially developed delayed cerebral vasospasm after receiving the placebo treatment in the first part of the study. They found that 50% of those patients who were in this group had their vasospasm subsequently reversed. As there is no placebo included, it is difficult to be sure that this could be definitively attributed to the treatment (Romesburg, 2009, p. 110).

5.2.2 Enoxaparin
Stein *et al.* (2006, p. 2) argue that vasospasm is not the sole contributing factor to development of delayed cerebral ischaemia, but that thromboembolism also has a role. Use of enoxaparin may therefore reduce ischaemia by blocking the clotting pathways. Only one clinical trial has been conducted to evaluate the effects of enoxaparin on delayed cerebral vasospasm. The study by Siironen *et al.* (2003, p. 953) found enoxaparin was not associated with any significant difference in function of patients at 3 months after SAH, according to either GCS or Rankin scale evaluation . This study was limited to patients who had already received other treatments, including nimodipine, triple H therapy and surgical evacuation. Therefore the results may not be generalizable to the entire population of patients at risk of delayed cerebral vasospasm (Gosall & Gosall, 2012, p. 54). Importantly, however, the study also found that some patients suffered additional bleeding after enoxaparin administration. Although the risk of this compared to placebo was not formally evaluated, the potential risk could be sufficient as to ethically prohibit the initiation of further studies of enoxaparin's use in this context (Howell, 2010, p. 43).

5.2.3 Free Radical Scavengers and Antioxidant Agents
Studies in rabbit models have shown the potential for edaravone in increasing the diameter of cerebral vessels once in spasm (Munakata *et al.*, 2011, p. 17). In their study focusing on prevention, Saito *et al.* (1998, p. 269) also found there to be a significantly reduced incidence of ischaemic deficit in those treated with ebselen at 3 months after SAH. This should constitute strong evidence, as it was derived from a double-blind, multicentre trial. However, this is not sufficient evidence alone to recommend this treatment approach for all patients over those treatments already available, without comparative studies.

5.2.4 Nitric Oxide Donors
Given the likely role of nitric oxide depletion in mediating cerebral vasospasm, there has been significant interest in increasing the nitric oxide available to cells in the area of the bleed. As nitric oxide has a very short half-life, the best means of achieving this is via nitric oxide donors (Fathi *et al.*, 2011, p. 93). They have been shown in animal models to reverse vasospasm with no significant side effects (Tierney *et al.*, 2001, p. 945).

Thomas and Rosenwasser (1999, p. 48) described three patients who were treated for vasospasm using sodium nitroprusside, after their vasospasm proved refractory to other interventions. They found that in all cases the NO donor was able to generate prompt and complete reversal of the vasospasm. This included resolution of neurological deficit and improvement in vasospasm on angiography and TCD US scanning.

Agrawal *et al.* (2009, p. 5) examined a slightly larger sample, containing 20 patients. They found that the 10 patients receiving sodium nitroprusside had improved cerebral blood flow and improved neurological status, as measured by the Glasgow Coma Score (GCS). As patients were not

randomised, this could potentially indicate some selection and treatment bias, as it is possible that certain traits led some patients to be in the treatment group (Barton, 2000, p. 255; Glasser, 2008, p. 23). Reinert *et al.* (2004, p. 435) also found that nitroglycerin was able to exert an effect, reducing blood pressure yet simultaneously improving cerebral blood flow. Although this study was of slightly higher quality, due to randomisation of subjects, the sample size was still relatively small for deriving good quality conclusions (Schulz & Grimes, 2005, p. 1348).

Although there have been some positive results from studies, there have been noted to be serious side effects associated with conventional nitric oxide donors, leading to exploration of the potential for novel nitric oxide donors (Fathi *et al.*, 2011, p. 93). There have yet to be any trials in humans of these potential new therapies, however.

5.3 Ongoing Research and Promising Novel Therapy

Dorsch (2002, pp. 131-132) also describes a number of experimental therapies which are being trialled for treatment of delayed cerebral vasospasm. Some have been further developed since this paper was published, but others are still relatively experimental.

Glyceryl nonivamide is a chemical which dilates vessels by release of calcitonin related peptide (Lin *et al.*, 2007, p. 877). This is still relatively novel and has not been well-described. Another alternative which also relates to calcitonin is gene transfer of calcitonin gene-related peptide. Calcitonin is a potent vasodilator and rabbit models have suggested that this novel treatment approach may prevent vasoconstriction (Toyoda *et al.*, 2000, p. 818), although this does not necessarily show it would reduce vasospasm in human patients.

Gene therapy is also being explored with induction of heme oxygenase-1 by adenovirus-mediated gene transfection. Studies have shown that this leads to reduced cerebral arterial contraction and therefore demonstrates potential for reducing risk of vasospasm (Ono *et al.*, 2002, p. 1094).

There are numerous other cell signalling pathways which have been increasingly supported in the literature as playing a role in cerebral vasospasm (Koide *et al.*, 2011, p. 145; Hollenberg, 2012, p. 103; Song *et al.*, 2013, p. 2063). Yet drugs to modify these pathways are not yet readily available (Zubkov *et al.*, 2003, p. 47).However, these could also be a further source of novel therapies in the future.

Other studies have focused on evaluating the use of known vasodilators that could be transferrable to cerebral vessels. For example, it is known that estrogen is a potent vasodilator – *in vivo* and animal model studies have shown it promoted vasodilation and reduces endothelin-1. It has also been shown to exert a neuroprotective effect from scavenging free radicals (Ding *et al.*, 2014, pp. 3-4). However, this is currently lacking trials in human patients.

Finally, molecular immunology, targeting the leukocyte-endothelial interactions which underlie vasospasm, by acting on cell adhesion molecules such as selectins and integrins, is also a further area for possible therapeutic development. However, this is an area that is still very much experimental and there is as yet nothing from human trials (Chaicana *et al.*, 2010, p.37).

6. Conclusions and Recommendations

One of the main difficulties in predicting, preventing and treating cerebral vasospasm after SAH is that it results from a complex interplay of different mechanical, inflammatory and chemical signalling pathways. Therefore there are multiple targets for therapeutic intervention, although with some producing better improvements in clinical symptoms and patient outcomes than others. Current treatment approaches are focused on prevention, with triple H therapy and calcium channel blockers amongst the most commonly applied interventions for prophylaxis. Although there is evidence that both in isolation are useful, it would seem that using both together could reduce the risk of vasospasm in a significant number of patients. This does not require intra-arterial infusion, as there is good evidence for both oral and IV calcium channel blockers, which may be more readily administered. Of the other therapies which are available, there is also good evidence to support the use of tirilazad and magnesium, both of which have also been shown to be safe. In spite of good evidence for statins, they are associated with a greater risk of adverse effects, so may not be preferential as first-line treatment. There is much less convincing evidence for the other interventions discussed, although it is possible that further studies into fasudil, albumin, enoxaparin, thromboxane synthetase inhibitors and free radical scavengers. However, at present, patients should not be given these agents in place of others for which there is a stronger evidence base.

There are currently fewer options for those patients who do go on to develop vasospasm. At present, the evidence seems to support the continued preference for balloon angioplasty as the first line treatment, or

calcium channel blockers for whom this is not suitable. Although triple H therapy is also currently used, there is no evidence to support this, so it would be recommended that this is not used for those patients who already have vasospasm, but only as an early preventive measure. While other treatments have been explored, there is currently insufficient evidence to recommend any of these in practice, although future studies, particularly focusing on free radical scavengers and some of the novel therapies discussed, could yield improvements in the ability to improve clinical outcomes for these patients.

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Appendix 1: Odds ratios calculated for studies
Clinical vasospasm – Egge *et al.* (2001, p. 598)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	5	4
	Did not develop vasospasm	11	12
	TOTAL	16	16

Odds ratio = 1.3636 (95% CI 0.2898, 6.4156)

Clinical vasospasm – Haley *et al.* (1993, p. 537)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	144	210
	Did not develop vasospasm	305	247
	TOTAL	449	457

Odds ratio = 0.5553 (95% CI 0.4237, 0.7277)

Clinical vasospasm – Kasuya *et al.* (2005, p. 895)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	4	3
	Did not develop vasospasm	65	25
	TOTAL	69	28

Odds ratio = 0.5128 (95% CI 0.1071, 2.4562)

Clinical vasospasm – Tseng *et al.* (2009, p. 171)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	11	16
	Did not develop vasospasm	29	24
	TOTAL	40	40

Odds ratio = 0.5690 (95% CI 0.2225, 1.4552)

Clinical vasospasm - Kassell *et al.* (1996, pp. 223-224)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	46	66
	Did not develop vasospasm	210	187
	TOTAL	256	253

Odds ratio = 1.6113 (95% CI 1.0535, 2.4644)

Clinical vasospasm - Haley *et al.* (1997, pp. 469-471)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	33	33
	Did not develop vasospasm	266	267
	TOTAL	299	300

Odds ratio = 0.9963 (95% CI 0.5973, 1.6616)

Clinical vasospasm – Lanzino *et al.* (1999, pp. 1012-1014)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	13	18
	Did not develop vasospasm	392	396
	TOTAL	405	414

Odds ratio = 0.7269 (95% CI 0.3527, 1.5093)

Clinical vasospasm – Lanzino & Kassell (1999, pp. 1020-1022)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	35	38
	Did not develop vasospasm	375	375
	TOTAL	410	413

Odds ratio = 0.9211 (95% CI 0.5694, 1.4900)

Clinical vasospasm - Lynch *et al.* (2005, p. 2024)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	5	12
	Did not develop vasospasm	14	8
	TOTAL	19	20

Odds ratio 0.2381 (95% CI 0.0613, 0.9254)

Clinical vasospasm - Lynch *et al.* (2005, p. 2024)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	5	12
	Did not develop vasospasm	14	8
	TOTAL	19	20

Odds ratio 0.2381 (95% CI 0.0613, 0.9254)

Clinical vasospasm - Tseng *et al.* (2005, p. 1630)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	17	25
	Did not develop vasospasm	23	15
	TOTAL	40	40

Odds ratio 0.4435 (95% CI 0.1810, 1.0864)

Clinical vasospasm - Vergouwen *et al.* (2005, p. 1451)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	13	11
	Did not develop vasospasm	3	5
	TOTAL	16	16

Odds ratio 1.9697 (95% CI 0.3816, 10.1665)

Clinical vasospasm - Chou *et al.* (2008, p. 2893)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	13	10
	Did not develop vasospasm	6	10
	TOTAL	19	20

Odds ratio 2.1667 (95% CI 0.5873, 7.9933)

Clinical and angiographic vasospasm - Kramer *et al.* (2008, p. 422)

		Treatment Group	
		Treatment	**Control**
Outcome – Clinical	**Developed vasospasm**	23	20
	Did not develop vasospasm	48	59
	TOTAL	71	79
Outcome - Angiographic	**Developed vasospasm**	29	33
	Did not develop vasospasm	42	46
	TOTAL	71	79

Clinical: Odds ratio 1.4135 (95% CI 0.6949, 2.8754)
Angiographic: Odds ratio 0.9625 (95% CI 0.5019, 1.8456)

Clinical vasospasm – Kirkpatrick *et al.* (2014, p. 671)

		Treatment Group	
		Treatment	**Control**
Outcome - Clinical	**Developed vasospasm**	64	67
	Did not develop vasospasm	327	345
	TOTAL	391	412
Outcome - Angiographic	**Developed vasospasm**	61	71
	Did not develop vasospasm	330	341
	TOTAL	391	412

Clinical: Odds ratio 1.0078 (95% CI 0.6930, 1.4656)
Angiographic: Odds ratio 0.8878 (95% CI 0.6107, 1.2906)

Angiographic vasospasm – Veyna *et al.* (2002, p. 510)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	6	5
	Did not develop vasospasm	14	11
	TOTAL	20	16

Odds ratio = 0.9429 (95% CI 0.2266, 3.9225)

Clinical vasospasm – van den Bergh *et al.* (2005, p. 1014)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	22	35
	Did not develop vasospasm	117	109
	TOTAL	139	144

Odds ratio = 0.5865 (95% CI 0.3234, 1.0603)

Clinical vasospasm – Wong *et al.* (2006, p. 142)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	7	13
	Did not develop vasospasm	23	17
	TOTAL	30	30

Odds ratio 0.3980 (95% CI 0.1309, 1.2105)

Clinical vasospasm – Wong *et al.* (2010, p. 923)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	42	29
	Did not develop vasospasm	127	129
	TOTAL	169	158

Odds ratio 1.4711 (95% CI 0.8634, 2.5065)

Clinical vasospasm – Muroi *et al.* (2008, p. 36)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	12	10
	Did not develop vasospasm	19	17
	TOTAL	31	27

Odds ratio 1.0737 (95% CI 0.3704, 3.1120)

Clinical vasospasm – Chia *et al.* (2002, p. 279)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	2	7
	Did not develop vasospasm	11	3
	TOTAL	13	10

Odds ratio 0.0779 (95% CI 0.0103, 0.5902)

Clinical vasospasm – Shaw *et al.* (2000, p. 995)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	56	67
	Did not develop vasospasm	151	146
	TOTAL	207	213

Odds ratio 0.8081 (95% CI 0.5302, 1.2319)

Clinical vasospasm – Vajkoczy *et al.* (2005, p. 9)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	6	15
	Did not develop vasospasm	9	2
	TOTAL	15	17

Odds ratio 0.0889 (95% CI 0.0147, 0.5383)

Clinical vasospasm – Macdonald *et al.* (2008, p. 3015)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	18	56
	Did not develop vasospasm	78	40
	TOTAL	96	96

Odds ratio = 0.1648 (95% CI 0.0857, 0.3169)

Clinical vasospasm – Shibuya *et al.* (1992, p. 571)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	69	79
	Did not develop vasospasm	26	17
	TOTAL	95	96

Odds ratio 0.5711 (95% CI 0.2860, 1.1402)

Clinical vasospasm – Zhao *et al.* (2006, p. 421)

		Treatment Group	
		Treatment	**Control**
Out come	**Developed vasospasm**	5	9
	Did not develop vasospasm	28	23
	TOTAL	33	32

Odds ratio 0.4563 (95% CI 0.1341, 1.5527)

Clinical vasospasm – Hamada *et al.* (2003, p. 2549)

		Treatment Group	
		Treatment	**Control**
Out come	**Developed vasospasm**	5	16
	Did not develop vasospasm	52	37
	TOTAL	57	53

Odds ratio 0.2224 (95% CI 0.0748, 0.6607)

Clinical vasospasm – Wurm *et al.* (2004, p. 97)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	5	40
	Did not develop vasospasm	52	20
	TOTAL	57	60

Odds ratio = 0.0481 (95% CI 0.0166, 0.1392)

Clinical vasospasm – Saito *et al.* (1998, p. 269)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	52	58
	Did not develop vasospasm	93	83
	TOTAL	145	141

Odds ratio 0.8001 (95% CI 0.4965, 1.2895)

Clinical vasospasm – Saito *et al.* (1998, p. 269)

		Treatment Group	
		Treatment	**Control**
Outcome	**Developed vasospasm**	52	58
	Did not develop vasospasm	93	83
	TOTAL	145	141

Odds ratio 0.8001 (95% CI 0.4965, 1.2895)