Review Article

Lower incidence of cerebral infarction correlates with improved functional outcome after aneurysmal subarachnoid hemorrhage

Mervyn DI Vergouwen[1,4], Nima Etminan[2,4], Don Ilodigwe[3] and R Loch Macdonald[3]

[1]Department of Experimental Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [2]Department of Neurosurgery, Heinrich-Heine University, Düsseldorf, Germany; [3]Division of Neurosurgery, St Michael's Hospital, Labatt Family Centre of Excellence in Brain Injury and Trauma Research, Keenan Research Centre of the Li Ka Shing Knowledge Institute of St Michael's Hospital and Department of Surgery, University of Toronto, Toronto, Ontario, Canada

Despite an undisputed association between vasospasm and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage (SAH), there is debate if this association implies causality. It has been suggested that cerebral infarction is a better outcome measure than vasospasm in clinical trials and observational studies. To further investigate the relationship between infarction and outcome, we performed a systematic review and meta-analysis of all randomized, double-blind, placebo-controlled trials that studied the efficacy of pharmaceutical preventive strategies in SAH patients, and had both cerebral infarction and clinical outcome as outcome events. Effect sizes were expressed in (pooled) risk ratio (RR) estimates with corresponding 95% confidence intervals (CIs). Sensitivity analyses were performed for studies with a low risk of bias and for those who reported outcome at 3 months after SAH. Twenty-four studies including 8,552 patients were included. Pharmaceutical treatments decreased the incidence of both cerebral infarction (RR: 0.83; 95% CI: 0.74 to 0.93) and of poor functional outcome (RR: 0.92; 95% CI: 0.86 to 0.98). The sensitivity analyses did not change the results essentially. These data suggest that the previously observed association between cerebral infarction and functional outcome implies causality, and that cerebral infarction is a better outcome measure than vasospasm in clinical trials and observational studies.

Introduction

Patients with aneurysmal subarachnoid hemorrhage (SAH) are at high risk of developing delayed cerebral ischemia (DCI). Delayed cerebral ischemia can progress to cerebral infarction, resulting in severe disability or death in 50% of patients. The pathogenesis of DCI remains incompletely understood. Despite the undisputed association between arterial narrowing ('vasospasm') and DCI, there is debate if this association implies causality (Millikan, 1975).

Many randomized controlled trials have been performed over the last decades aiming to find a treatment that effectively prevents DCI. Although several drugs were identified that successfully prevent vasospasm, no effects on clinical outcome were observed (Macdonald *et al*, 2008; Etminan *et al*, 2011). It has been proposed that cerebral infarction and functional outcome, and not vasospasm, should be the main outcome measures in clinical trials and observational studies (Vergouwen *et al*, 2010). The aim of the present study was to investigate if a lower incidence of cerebral infarction after SAH correlates with better functional outcomes.

Materials and methods

For this systematic review, the Cochrane Collaboration format was used (Higgins and Green, 2008).

Correspondence: Dr MDI Vergouwen, Department of Experimental Vascular Medicine, G1-145, Academic Medical Center, University of Amsterdam, Meibergdreef 9, Amsterdam 1105 AZ, The Netherlands.
E-mail: m.d.vergouwen@amc.uva.nl
[4]These authors contributed equally to this work.

Selection Criteria

Types of studies: All randomized, double-blind, placebo-controlled trials that studied the efficacy of pharmaceutical strategies aiming to prevent cerebral infarction and poor outcome in SAH patients were included, regardless of type and dosage of drug and follow-up duration.

Types of outcome measures: Only trials that included both cerebral infarction and clinical outcome as outcome events were included.

Definition of outcome measures: Cerebral infarction was defined as 'the presence of cerebral infarction on computed tomography (CT) or magnetic resonance scan of the brain within 6 weeks after SAH, or on the latest CT or magnetic resonance scan made before death within 6 weeks, or proven at autopsy, not present on the CT or magnetic resonance scan between 24 and 48 hours after early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment. Hypodensities on CT imaging resulting from ventricular catheter or intraparenchymal hematoma should not be regarded as cerebral infarctions from DCI' (Vergouwen et al, 2010). Poor clinical outcome was defined as severe disability, vegetative state or death, as defined by the investigators of the individual studies, either measured with the modified Rankin scale or (extended) Glasgow outcome scale. If the investigators provided data on the individual categories of the used outcome scales, we considered a modified Rankin scale of 3 to 6 or a Glasgow outcome scale of 1 to 3 as poor clinical outcome. In those studies where an inverted Glasgow outcome scale was used, poor clinical outcome was readjusted to the original scale. For all included studies, we used data from the last blinded outcome measurement. If the study only provided a figure or the percentage of patients with an outcome event, the actual numbers were calculated from the figure or percentages.

Search strategy for identification of studies: Two of the authors (NE and MDIV) conducted a systematic search of the literature using the Pubmed database (http://www.ncbi.nlm.nih.gov/pubmed) up to February 2011 (week 8) for the variable 'SAH.' The search was limited to 'clinical trials,' 'controlled clinical trials,' and 'human studies.' Abstracts of the resulting studies were reviewed independently and invalid studies were excluded in a three-step manner. In the fourth and final step, only double-blinded, placebo-controlled, randomized studies were screened for valid end points, that is cerebral infarction and functional outcome. Further, additional studies in previous meta-analyses that investigated the efficacy of pharmaceutical interventions to prevent cerebral infarction after SAH were searched.

Statistics

Data were processed in Review manager 5.0.25 as supplied by the Cochrane Collaboration. Effect sizes were expressed in (pooled) risk ratio (RR) estimates. Statistical uncertainty was expressed in 95% confidence intervals (CIs). Pooled data were interpreted to be heterogeneous in case the probability value of the χ^2 test was $\leqslant 0.10$. If no heterogeneity could be demonstrated, we used a fixed-effects model. Otherwise, a random-effects model was used. Two authors (MDIV and NE) independently assessed risk of bias by reviewing methodological quality of the included studies for allocation concealment and blinding. Funnel plots, including Begg's and Egger's statistical tests, were generated in Stata (version 9, College Station, TX, USA) to investigate potential bias. Sensitivity analyses were performed for studies with a low risk of bias (both on the items 'allocation concealment' and 'blinding'), and for studies that reported functional outcome at 3 months after SAH.

Results

The initial search yielded 780 articles, of which ultimately 756 were excluded. The remaining 24 trials were included in the analysis, including 8,552 patients (Macdonald et al, 2008; Asano et al, 1996; Chou et al, 2008; Gomis et al, 2010; Haley et al, 1993, 1997; Hop et al, 2000; Kassell et al, 1996; Lanzino et al, 1999; Lanzino and Kassell, 1999; Ohman and Heiskanen, 1988; Petruk et al, 1988; Pickard et al, 1989; Saito et al, 1998; Shaw et al, 2000; Shibuya et al, 1992; Siironen et al, 2003; Juvela et al, 2005; Springborg et al, 2007; Suzuki et al, 1989; Tseng et al, 2009; van den Bergh et al, 2005, 2006; Westermaier et al, 2010; Wong et al, 2010, 2011). A total of 4,818 patients were randomized to pharmaceutical treatment, and 3,734 patients to placebo. Characteristics of the included studies are listed in Table 1.

Analyses

For the analysis of cerebral infarction, data from 7,982 patients were available (4,508 patients randomized to pharmaceutical treatment and 3,474 to placebo). The overall number of patients with cerebral infarction was 1,282 in the group of patients randomized to pharmaceutical treatment and 1,182 in the placebo group. Our meta-analysis demonstrated a significant and favorable effect of treatment compared with placebo on cerebral infarction (pooled RR: 0.83; 95% CI: 0.74 to 0.93). Heterogeneity between the trials was high ($I^2 = 58\%$ and $P = 0.0002$), which justified the use of a random-effects meta-analysis model (Figure 1).

For clinical outcome, most studies used the Glasgow outcome scale (Macdonald et al, 2008; Asano et al, 1996; Gomis et al, 2010; Haley et al, 1993, 1997; Kassell et al, 1996; Lanzino et al, 1999; Lanzino and Kassell, 1999; Ohman and Heiskanen, 1988; Petruk et al, 1988; Pickard et al, 1989; Saito et al, 1998; Shaw et al, 2000; Shibuya et al, 1992; Siironen et al, 2003; Springborg et al, 2007; Westermaier et al, 2010; Wong et al, 2010) or modified Rankin scale (Chou et al, 2008; Hop et al, 2000;
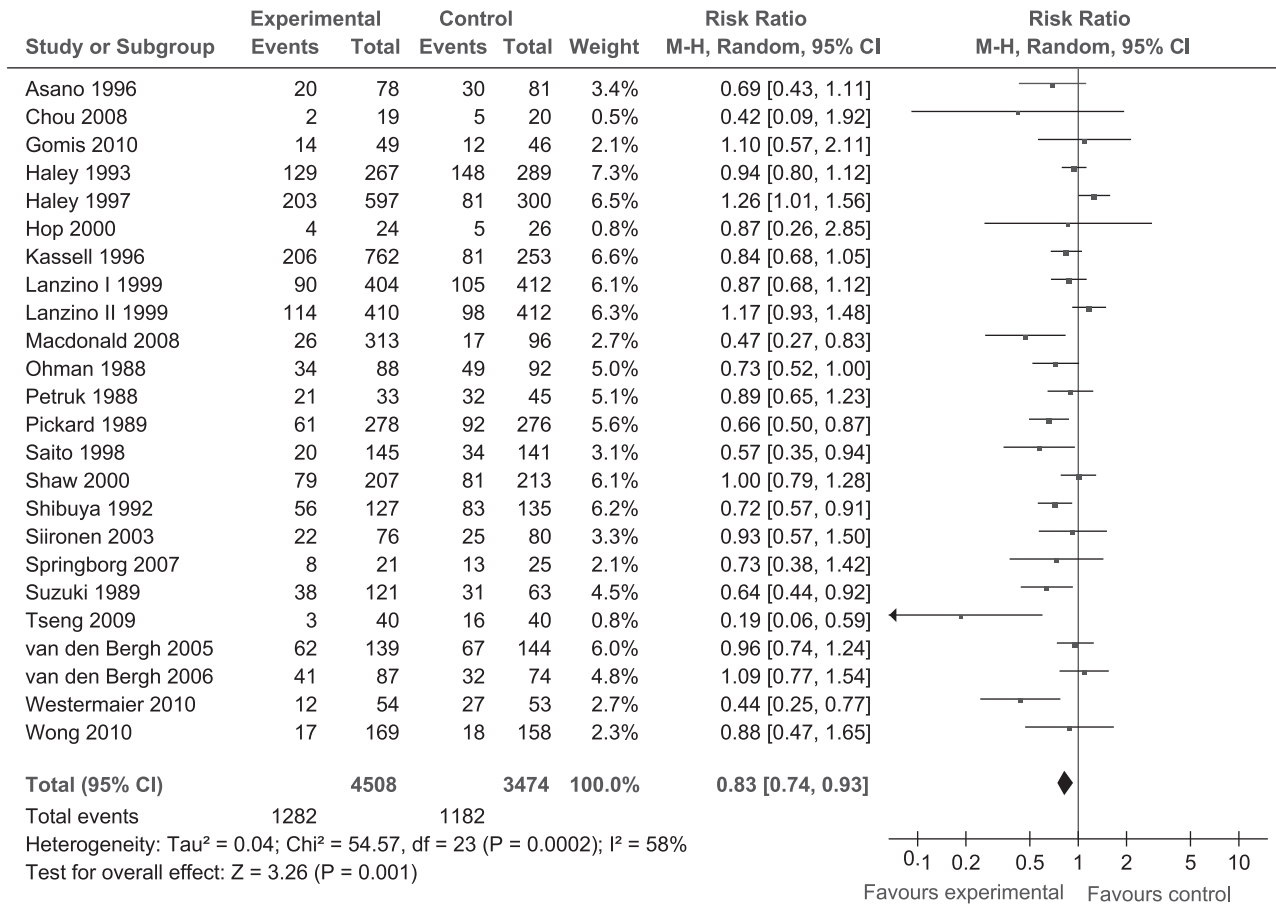
Table 1 Characteristics of included studies

Study	Drug studied	Imaging modality	Definition of cerebral infarction	Definition of poor outcome	Adequate allocation concealment	Adequate blinding
Asano *et al* (1996)	AVS	CT	All patients were required to undergo repeat CT scans on completion of treatment (~day 14) and at ~day 30, in addition to those routinely obtained on admission, immediately after surgery, or on exacerbation of neurologic deficits. The findings of each CT scan and the presumed cause of the postoperative appearance of LDAs were documented according to the surgeon's judgment	GOS 1–3 at 3 months	Yes	Yes
Chou *et al* (2008)	Simvastatin	CT or MRI	The development of a new lesion consistent with infarction on CT or MRI in the vascular territory of angiographic or TCD vasospasm (timing of imaging unclear)	mRS 3–6 on discharge	Unclear	Unclear
Gomis *et al* (2010)	Methyl-prednisolone	CT	A new ischemic area following vasospasm was defined as any new low-density zone on CT scan not explained by other causes of focal cerebral ischemia between 4 and 10 days after SAH onset	GOS 1–3 at 12 months	Unclear	Yes
Haley *et al* (1993)	Nicardipine	CT	Infarction on a CT scan obtained at 3 months	GOS 1–3 at 3 months	Yes	Yes
Haley *et al* (1997)	Tirilazad	CT	A follow-up CT scan of the head was obtained at 3 months and sent to the Central Registry for blinded interpretation and measurement of infarct volume using planimetric techniques	GOS 1–3 at 3 months	Unclear	Yes
Hop *et al* (2000)	Aspirin	CT	New hypodense lesion consistent with clinical signs of delayed cerebral ischemia	mRS 3–6 at 4 months	Yes	Yes
Kassell *et al* (1996)	Tirilazad	CT	A follow-up CT scan of the head was obtained at 3 months and sent to the Central Registry for blinded interpretation and measurement of infarct volume using planimetric techniques	GOS 1–3 at 3 months	Unclear	Yes
Lanzino *et al* (1999)	Tirilazad	CT	Unclear	GOS 1–3 at 3 months	Unclear	Yes
Lanzino and Kassell (1999)	Tirilazad	CT	Unclear	GOS 1–3 at 3 months	Unclear	Yes
Macdonald *et al* (2008)	Clazosentan	CT	New cerebral infarct due to vasospasm within 6 weeks of SAH	GOS 1–3 at 12 weeks	Yes	Yes
Öhman and Heiskanen (1988)	Nimodipine	CT	Unclear	GOS 1–3 at 3 months	Unclear	Unclear
Petruk *et al* (1988)	Nimodipine	CT	Hypodense areas consistent with infarction were categorized at 3 months as being (1) in the same area as a previous ICH; (2) secondary to vasospasm if they occurred in an area where there had not been a previous ICH; or (3) indeterminate, if no previous CT scan was available or if they were not easily placed into one of the previous two categories	GOS 1–3 at 3 months	Yes	Yes
Pickard *et al* (1989)	Nimodipine	CT	The diagnosis of infarction was classified as definitive or probable according to whether confirmatory evidence was available from CT or at necropsy	GOS 1–3 at least 3 months after entry to the trial	Yes	Yes
Saito *et al* (1998)	Ebselen	CT	LDAs on CT scans obtained around day 14 or day 30 after SAH. LDAs that appeared within 2 days of surgery or within 24 hours of onset and were considered to be caused by surgery, and temporary	GOS 1–3 at 3 months	Unclear	Unclear

Table 1 *Continued*

Study	Drug studied	Imaging modality	Definition of cerebral infarction	Definition of poor outcome	Adequate allocation concealment	Adequate blinding
			clipping or intracerebral hematoma were excluded from assessment			
Shaw *et al* (2000)	TAK-044	CT or postmortem studies	Development of a cerebral infarct visualized on a CT scan or at autopsy during the 3 months following onset of SAH	GOS 1–3 at 3 months	Yes	Yes
Shibuya *et al* (1992)	Fasudil	CT	Larger LDAs (due to vasospasm) between two CT scans (obtained at 1 or 2 weeks after the SAH, and at 1 month)	GOS 1–3 at 1 month	Yes	Yes
Siironen *et al* (2003)	Enoxaparin	CT	A hypodense lesion, caused by delayed cerebral ischemia (with or without symptoms and after excluding other causes) and appearing later than on the 1st postoperative CT scan	GOS 1–3 at 3 months	Unclear	Yes
Springborg *et al* (2007)	Erythropoietin	CT or MRI	CT or MRI scans performed around day 14 after the hemorrhage were evaluated for signs of vasospastic infarction	GOS 1–3 at 6 months	Yes	Yes
Suzuki *et al* (1989)	OKY-046	CT	Abnormal low densities (LD) with 48 hours postoperatively and after 21 days were classified into five grades: −=no LD; +=small definite lacunar infarction; ++=moderate infarction larger than 2 cm but smaller than the territory of one vessel; +++=multiple small-to-moderate infarctions; ++++=large infarction over the entire MCA territory or extended territories of several vessels. All grades were included in the analysis	Functional ADL was evaluated at 1 and 3 months after aneurysmal rupture by of nine grades (0=normal; 1=almost normal; 2=slight neurologic deficit with usable hand finger; 3=unaided daily life; 4=assisted daily life; 5=can leave bad with assistance; 6=confined to bed; 7=vegetative state; 8=deceased at 3 months. Grades 4–8 were considered poor functional outcome	Unclear	Unclear
Tseng *et al* (2009)	Erythropoietin	CT	Unclear	mRS 4–6, GOS 1–3 or NIHSS >20 at 6 months	Yes	Yes
Van den Bergh *et al* (2005)	Magnesium sulfate	CT	Any new hypodensity on brain CT regardless of its cause	mRS 4–6 at 3 months	Yes	Yes
Van den Bergh *et al* (2006)	Aspirin	CT	Any new hypodensity on brain CT, regardless of its cause	mRS 4–6 at 3 months	Yes	Yes
Westermaier *et al* (2010)	Magnesium sulfate	CT	Parenchymal hypodensity appearing between day 3 and the end of the observation period	GOS 1–3 at 6 months	Unclear	Yes
Wong *et al* (2010)	Magnesium sulfate	Unclear	A new cerebral infarction within 3 weeks that was not related to posttreatment (coiling or clipping) complications, the ventricular catheter track, a rebleed, or hydrocephalus	GOSE 1–4 at 6 months	Yes	Yes

ADL, activity in daily living; AVS, (±)-*N*,*N*'-propylenedinicotinamide (nicaraven); CT, computed tomography; GOS, Glasgow outcome score; GOSE, extended Glasgow outcome score; ICH, intracerebral hemorrhage; LDAs, low-density areas; MCA, middle cerebral artery; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; SAH, subarachnoid hemorrhage; TCD, transcranial Doppler.

| Study or Subgroup | Experimental | | Control | | Weight | Risk Ratio | Risk Ratio |
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Asano 1996	20	78	30	81	3.4%	0.69 [0.43, 1.11]	
Chou 2008	2	19	5	20	0.5%	0.42 [0.09, 1.92]	
Gomis 2010	14	49	12	46	2.1%	1.10 [0.57, 2.11]	
Haley 1993	129	267	148	289	7.3%	0.94 [0.80, 1.12]	
Haley 1997	203	597	81	300	6.5%	1.26 [1.01, 1.56]	
Hop 2000	4	24	5	26	0.8%	0.87 [0.26, 2.85]	
Kassell 1996	206	762	81	253	6.6%	0.84 [0.68, 1.05]	
Lanzino I 1999	90	404	105	412	6.1%	0.87 [0.68, 1.12]	
Lanzino II 1999	114	410	98	412	6.3%	1.17 [0.93, 1.48]	
Macdonald 2008	26	313	17	96	2.7%	0.47 [0.27, 0.83]	
Ohman 1988	34	88	49	92	5.0%	0.73 [0.52, 1.00]	
Petruk 1988	21	33	32	45	5.1%	0.89 [0.65, 1.23]	
Pickard 1989	61	278	92	276	5.6%	0.66 [0.50, 0.87]	
Saito 1998	20	145	34	141	3.1%	0.57 [0.35, 0.94]	
Shaw 2000	79	207	81	213	6.1%	1.00 [0.79, 1.28]	
Shibuya 1992	56	127	83	135	6.2%	0.72 [0.57, 0.91]	
Siironen 2003	22	76	25	80	3.3%	0.93 [0.57, 1.50]	
Springborg 2007	8	21	13	25	2.1%	0.73 [0.38, 1.42]	
Suzuki 1989	38	121	31	63	4.5%	0.64 [0.44, 0.92]	
Tseng 2009	3	40	16	40	0.8%	0.19 [0.06, 0.59]	
van den Bergh 2005	62	139	67	144	6.0%	0.96 [0.74, 1.24]	
van den Bergh 2006	41	87	32	74	4.8%	1.09 [0.77, 1.54]	
Westermaier 2010	12	54	27	53	2.7%	0.44 [0.25, 0.77]	
Wong 2010	17	169	18	158	2.3%	0.88 [0.47, 1.65]	
Total (95% CI)		**4508**		**3474**	**100.0%**	**0.83 [0.74, 0.93]**	
Total events	1282		1182				

Heterogeneity: Tau² = 0.04; Chi² = 54.57, df = 23 (P = 0.0002); I² = 58%
Test for overall effect: Z = 3.26 (P = 0.001)

0.1 0.2   0.5   1   2   5   10
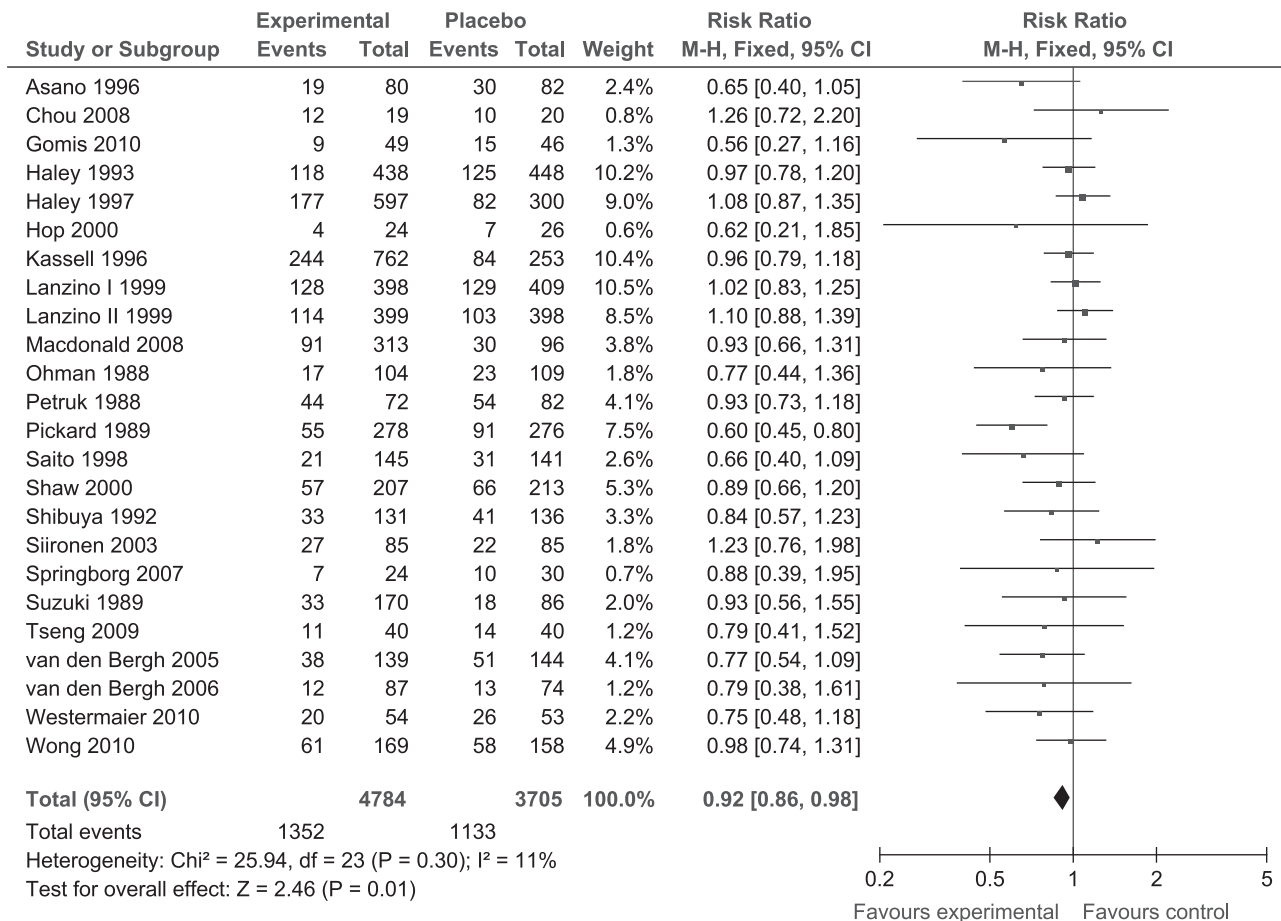Favours experimental   Favours control

Figure 1 (Pooled) risk ratio (RR) estimates for patients on pharmaceutical treatment to have cerebral infarction. CI, confidence interval.

Tseng *et al*, 2009; van den Bergh *et al*, 2005, 2006) (Table 1). One study used a functional activity in daily living scale (Suzuki *et al*, 1989). For the meta-analysis of poor clinical outcome, data from 8,489 patients were available (4,784 patients randomized to pharmaceutical treatment, 3,705 to placebo). The number of patients with poor outcome was 1,352 in the pharmaceutically treated group and 1,133 in the placebo group. Meta-analysis showed a beneficial effect of treatment compared with placebo on poor clinical outcome (pooled RR: 0.92; 95% CI: 0.86 to 0.98). Heterogeneity between the trials was not significant ($I^2 = 11\%$ and $P = 0.30$), which justified the use of a fixed-effects model (Figure 2).

Risk of Bias Assessments

For allocation concealment, risk of bias was low in 13 (Macdonald *et al*, 2008; Asano *et al*, 1996; Haley *et al*, 1993; Hop *et al*, 2000; Petruk *et al*, 1988; Pickard *et al*, 1989; Shaw *et al*, 2000; Shibuya *et al*, 1992; Springborg *et al*, 2007; Tseng *et al*, 2009; van den Bergh *et al*, 2005, 2006; Wong *et al*, 2010) and unclear in 11 studies (Chou *et al*, 2008; Gomis *et al*, 2010; Haley *et al*, 1997; Kassell *et al*, 1996; Lanzino

et al, 1999; Lanzino and Kassell, 1999; Ohman and Heiskanen, 1988; Saito *et al*, 1998; Siironen *et al*, 2003; Suzuki *et al*, 1989; Westermaier *et al*, 2010) (Table 1). For blinding, risk of bias was low in 20 studies (Macdonald *et al*, 2008; Asano *et al*, 1996; Gomis *et al*, 2010; Haley *et al*, 1993, 1997; Hop *et al*, 2000; Kassell *et al*, 1996; Lanzino *et al*, 1999; Lanzino and Kassell, 1999; Petruk *et al*, 1988; Pickard *et al*, 1989; Shaw *et al*, 2000; Shibuya *et al*, 1992; Siironen *et al*, 2003; Springborg *et al*, 2007; Tseng *et al*, 2009; van den Bergh *et al*, 2005, 2006; Westermaier *et al*, 2010; Wong *et al*, 2010), and unclear in four studies (Chou *et al*, 2008; Ohman and Heiskanen, 1988; Saito *et al*, 1998; Suzuki *et al*, 1989). High risk of bias was not observed in any of the studies. One of the authors of this systematic review acknowledges potential risk of bias, because he is an author of one of the studies included in this systematic review (Macdonald *et al*, 2008). Funnel plots are shown in Figures 3A and 3B. For the cerebral infarction outcome measure, the Egger's test supports the evidence of significant level of bias ($P = 0.037$) in the pooled publications. However, Begg's test ($P = 0.172$) and the close to symmetry orientation of the funnel plot (Figure 3A) suggested otherwise. For the poor clinical outcome measure,

Study or Subgroup	Experimental Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Asano 1996	19	80	30	82	2.4%	0.65 [0.40, 1.05]
Chou 2008	12	19	10	20	0.8%	1.26 [0.72, 2.20]
Gomis 2010	9	49	15	46	1.3%	0.56 [0.27, 1.16]
Haley 1993	118	438	125	448	10.2%	0.97 [0.78, 1.20]
Haley 1997	177	597	82	300	9.0%	1.08 [0.87, 1.35]
Hop 2000	4	24	7	26	0.6%	0.62 [0.21, 1.85]
Kassell 1996	244	762	84	253	10.4%	0.96 [0.79, 1.18]
Lanzino I 1999	128	398	129	409	10.5%	1.02 [0.83, 1.25]
Lanzino II 1999	114	399	103	398	8.5%	1.10 [0.88, 1.39]
Macdonald 2008	91	313	30	96	3.8%	0.93 [0.66, 1.31]
Ohman 1988	17	104	23	109	1.8%	0.77 [0.44, 1.36]
Petruk 1988	44	72	54	82	4.1%	0.93 [0.73, 1.18]
Pickard 1989	55	278	91	276	7.5%	0.60 [0.45, 0.80]
Saito 1998	21	145	31	141	2.6%	0.66 [0.40, 1.09]
Shaw 2000	57	207	66	213	5.3%	0.89 [0.66, 1.20]
Shibuya 1992	33	131	41	136	3.3%	0.84 [0.57, 1.23]
Siironen 2003	27	85	22	85	1.8%	1.23 [0.76, 1.98]
Springborg 2007	7	24	10	30	0.7%	0.88 [0.39, 1.95]
Suzuki 1989	33	170	18	86	2.0%	0.93 [0.56, 1.55]
Tseng 2009	11	40	14	40	1.2%	0.79 [0.41, 1.52]
van den Bergh 2005	38	139	51	144	4.1%	0.77 [0.54, 1.09]
van den Bergh 2006	12	87	13	74	1.2%	0.79 [0.38, 1.61]
Westermaier 2010	20	54	26	53	2.2%	0.75 [0.48, 1.18]
Wong 2010	61	169	58	158	4.9%	0.98 [0.74, 1.31]
Total (95% CI)		**4784**		**3705**	**100.0%**	**0.92 [0.86, 0.98]**
Total events	1352		1133			

Heterogeneity: Chi² = 25.94, df = 23 (P = 0.30); I² = 11%
Test for overall effect: Z = 2.46 (P = 0.01)

Figure 2 (Pooled) risk ratio (RR) estimates for patients on pharmaceutical treatment to have poor clinical outcome. CI, confidence interval.

both the Egger's test ($P = 0.037$) and Begg's test ($P = 0.038$) with the close to asymmetry orientation of the funnel plot (Figure 3B) support the evidence of significant level of bias.

Sensitivity Analyses

In the sensitivity analysis that only included studies with a low risk of bias, as assessed on the items 'allocation concealment' and 'blinding,' 13 studies were included with 3,831 patients (Macdonald et al, 2008; Asano et al, 1996; Haley et al, 1993; Hop et al, 2000; Petruk et al, 1988; Pickard et al, 1989; Shaw et al, 2000; Shibuya et al, 1992; Springborg et al, 2007; Tseng et al, 2009; van den Bergh et al, 2005, 2006; Wong et al, 2010). The pooled RR for cerebral infarction was 0.70 (95% CI: 0.56 to 0.88) and for poor outcome 0.78 (95% CI: 0.67 to 0.90) (figures not shown). Heterogeneity between the trials was significant in the cerebral infarction analysis ($I^2 = 45\%$ and $P = 0.04$), but not in the poor outcome analysis ($I^2 = 0\%$ and $P = 0.62$). In the sensitivity analysis that only included studies with an outcome assessment 3 months after SAH, 16 studies were included with

7,530 patients (Macdonald et al, 2008; Asano et al, 1996; Haley et al, 1993, 1997; Kassell et al, 1996; Lanzino et al, 1999; Lanzino and Kassell, 1999; Ohman and Heiskanen, 1988; Petruk et al, 1988; Pickard et al, 1989; Saito et al, 1998; Shaw et al, 2000; Siironen et al, 2003; Suzuki et al, 1989; van den Bergh et al, 2005, 2006). The pooled RR for cerebral infarction was 0.87 (95% CI: 0.78 to 0.98) and for poor outcome 0.93 (95% CI: 0.86 to 1.00) (figures not shown). Again, heterogeneity between the trials was high in the cerebral infarction analysis ($I^2 = 59\%$ and $P = 0.002$), but not in the poor outcome analysis ($I^2 = 28\%$ and $P = 0.14$).

Discussion

This systematic review including 8,552 patients shows that a lower incidence of cerebral infarction after SAH correlates with a lower incidence of poor functional outcome. The sensitivity analysis that only included studies with a low risk of bias confirmed these findings. The sensitivity analysis that reported on functional outcome 3 months after
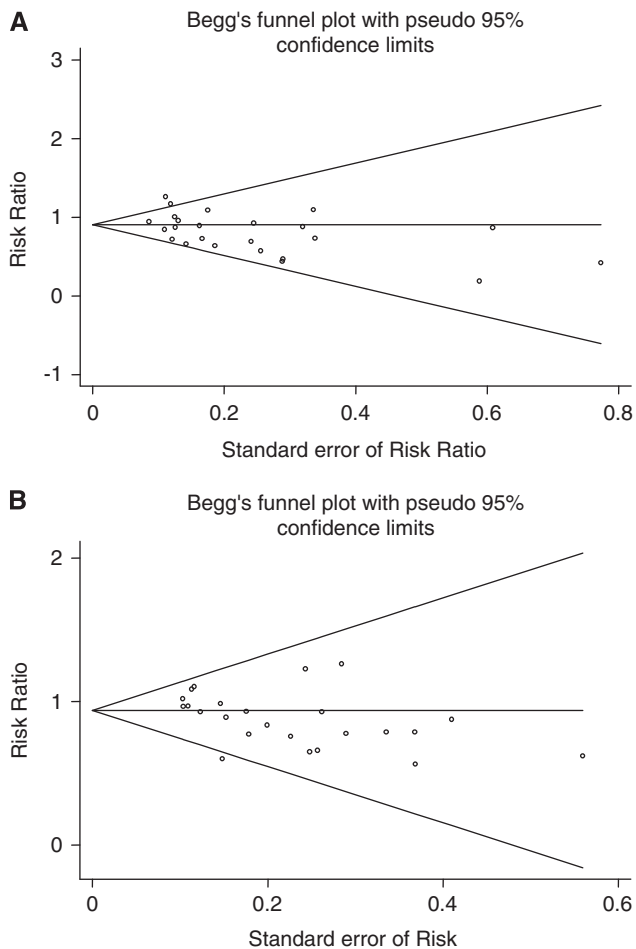
Figure 3 Funnel plot for outcome measure cerebral infarction (**A**) and functional outcome (**B**). The name funnel plot arises from the fact that precision of the estimated intervention effect increases as the size of the study increases. Effect estimates from small studies will therefore scatter more widely at the *y*-axis, with the spread narrowing among larger studies. In the absence of bias, the plot should approximately resemble a symmetrical funnel. If there is bias, from for example publication bias or studies with low methodological quality, this will lead to an asymmetrical appearance of the funnel plot (Higgins and Green, 2008).

SAH showed similar findings, though the poor outcome analysis had CIs that included 1.00.

Previous studies found strong associations between vasospasm, DCI, cerebral infarction, and poor functional outcome (Fisher *et al*, 1977; Vergouwen *et al*, 2011; Rabinstein *et al*, 2004; Fergusen and Macdonald 2007). However, associations do not always represent causal relationships. Especially for vasospasm, it is debated if it causes DCI and poor functional outcome (Millikan, 1975; Vergouwen *et al*, 2008). A recent systematic review including 4,235 patients with SAH showed that pharmaceutical interventions decreased vasospasm after SAH, but not poor functional outcome (Etminan *et al*, 2011). This dissociation between vasospasm and

clinical outcome could result from methodological problems, sample size, insensitivity of clinical outcome measures, or from mechanisms other than vasospasm that also contribute to poor outcome. Current understanding is that the pathogenesis of DCI is multifactorial. Microthromboembolism, cortical spreading ischemia, delayed effects of acute SAH-induced brain injury, and impaired cerebral autoregulation have been suggested to have a role in clinical outcome (Vergouwen *et al*, 2008; Dreier *et al*, 2009; Yundt *et al*, 1998). Since cerebral infarction is the ultimate outcome of DCI, it has been suggested that cerebral infarction is a better outcome measure in observational studies and clinical trials than vasospasm (Vergouwen *et al*, 2010). The findings of the present study support this suggestion. Obviously, the main outcome measure in such studies should be functional outcome (Vergouwen *et al*, 2010).

This study has some limitations. Significant heterogeneity was observed in the cerebral infarction meta-analyses. This might result from the many different drugs used in the various studies, which all have different pharmacological properties. The studies that were included did not use a uniform definition of cerebral infarction, which may introduce some variability. To account for the observed heterogeneity, we used a random-effects model instead of a fixed-effects model. In addition, the meta-analysis shows an association between cerebral infarction and poor outcome. As with the relation between angiographic vasospasm and DCI, it is still conceivable that this relation is not causal, although this seems unlikely since it would require one to accept that dead brain is not somehow detrimental to outcome. Furthermore, for the outcome measure 'functional outcome,' statistical tests showed evidence of bias. However, our sensitivity analysis that only included studies with low risk of bias confirmed our finding that lower rates of infarction are correlated with better functional outcomes. Finally, in many of the studies included in the meta-analysis, diagnosis of cerebral infarction was based on CT scans only. Since the sensitivity of CT to detect cerebral infarction is low, the result of the meta-analysis might significantly underestimate the presence of infarction (Dreier *et al*, 2002). Future studies should investigate the relationship between cerebral infarction on magnetic resonance imaging and functional outcome after SAH.

In conclusion, pharmaceutical treatments decreased both cerebral infarction and poor functional outcome after SAH. These data suggest that the previously observed association between cerebral infarction and functional outcome implies causality. Considering our prior meta-analysis studying the relationship between angiographic vasospasm and outcome that showed no relationship (Etminan *et al*, 2011), the present results suggest that cerebral infarction may be a better outcome measure than vasospasm in clinical trials and observational studies.

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Disclosure/conflict of interest

Dr RL Macdonald is a consultant for Actelion Pharmaceuticals and Chief Scientific Officer of Edge Therapeutics, Inc.

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