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INTERVENTIONAL

Treatment of cerebral vasospasm following aneurysmal subarachnoid haemorrhage: a systematic review and meta-analysis

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Abstract

Objectives To examine the clinical outcome of aneurysmal subarachnoid haemorrhage (aSAH) patients exposed to cerebral vasospasm (CVS)-targeted treatments in a meta-analysis and to evaluate the efficacy of intra-arterial (IA) approaches in patients with severe/refractory vasospasm.

Methods Randomised controlled trials, prospective and retrospective observational studies reporting clinical outcomes of aSAH patients exposed to CVS targeted treatments, published between 2006-2016 were searched using PubMed, EMBASE and the Cochrane Library. The main endpoint was the proportion of unfavourable outcomes, defined as a modified Rankin score of 3–6 at last follow-up.

Results Sixty-two studies, including 26 randomised controlled trials, were included (8,976 patients). At last follow-up 2,490 of the 8,976 patients had an unfavourable outcome, including death (random-effect weighted-average, 33.7%; 99% confidence interval [CI], 28.1–39.7%; Q value, 806.0; $I^2 = 92.7\%$). The RR of unfavourable outcome was lower in patients treated with Cilostazol (RR = 0.46; 95% CI, 0.25–0.85; $P = 0.001$; Q value, 1.5; $I^2 = 0$); and in refractory CVS patients treated by IA intervention (RR = 0.68; 95% CI, 0.57–0.80; $P < 0.0001$; number needed to treat with IA intervention, 6.2; 95% CI, 4.3–11.2) when compared with the best available medical treatment.

Conclusions Endovascular treatment may improve the outcome of patients with severe-refractory vasospasm. Further studies are needed to confirm this result.

Key Points

- *33.7% of patients with cerebral Vasospasm following aneurysmal subarachnoid-hemorrhage have an unfavorable outcome.*
- *Refractory vasospasm patients treated using endovascular interventions have lower relative risk of unfavourable outcome.*
- *Subarachnoid haemorrhage patients with severe vasospasm may benefit from endovascular interventions.*
- *The relative risk of unfavourable outcome is lower in patients treated with Cilostazol.*

Keywords Subarachnoid haemorrhage · Cerebral vasospasm · Delayed cerebral ischaemia · Endovascular treatment · Meta-analysis

Abbreviations

aSAH	Aneurysmal subarachnoid haemorrhage
CVS	Cerebral vasospasm
IA	Intra-arterial
DCI	Delayed cerebral ischaemia
GOS	Glasgow Outcome Scale

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GOSE GOS extended
RCT randomised controlled trial
TBA Transluminal balloon angioplasty
TCD Transcranial Doppler

Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) accounts for less than 5% of all strokes [1], but patient outcomes remain poor with mortality rates up to 45% and significant morbidity among survivors [2]. A major contributor to death and disability in aSAH survivors is cerebral vasospasm (CVS). Vasospasm is commonly treated using vasodilator-induced hypertension, to which intra-arterial (IA) intervention may be added in more severe or refractory cases. While only oral nimodipine has a level Ia indication for treatment of CVS, to date there is no randomised evidence of the efficacy of IA interventions in patients with severe vasospasm [3].

During the last decade, two studies [4, 5] have reviewed the effect of available classes of drugs on angiographic outcome after aSAH. However, these reviews did not take into account recent large international trials and studies on endovascular treatment. In addition, the outcome measure that was used in previous systematic reviews was angiographic [4, 5], rather than functional outcome [6].

Our aims were: (1) to report the clinical outcome of aSAH patients exposed to CVS-targeted treatments in a systematic review and meta-analysis, and (2) to compare the efficacy of intra-arterial (IA) and non-IA approaches in patients with severe refractory vasospasm.

Materials and methods

Before conducting the review, we developed a detailed protocol including objectives and plans for collecting and analysing data. The manuscript was prepared in accordance with the PRISMA guidelines [7, 8]. This study was designed, conducted and analysed, and the manuscript was written independently of industry. The search strategy is provided in online Electronic Supplementary Material (ESM) 1.

Selection criteria

The pre-specified inclusion criteria were: (1) explicitly reported mortality or permanent morbidity; (2) at least ten aSAH/CVS patients; (3) peer-reviewed original studies; (4) published in English or French between 2006 and 2016; (5) methodological score of ten or more.

Data extraction

Data were extracted by one author (G.B.) using a standardised critical appraisal and data-extraction form. A second author (O.N.) reviewed a random sample of 20% of the studies and the data extracted. The data extraction form was subdivided into five sections: (1) study characteristics, (2) baseline characteristics, (3) definition of vasospasm, (4) intervention or treatment and (5) clinical and imaging outcome measures (case fatality and unfavourable outcome). Please *see* ESM 2 for details on data extraction method.

Outcome measures

Favourable outcome was defined as no or moderate disability, including Glasgow Outcome Scale [9] (GOS) score <4, inverted GOS ≤2, GOS Extended [10] (GOSE) score ≤4, modified Rankin score [11] (mRs) ≤2 or explicit report of no/moderate disability. Unfavourable outcomes included severe disability, vegetative state, and death (mRs >2, GOS score >4, GOSE >4 or inverted GOS >2). Outcome was recorded for each study at the latest clinical follow-up (minimum 30 days).

Baseline characteristics of patients

Baseline data included gender, number and mean age of the eligible patients, initial clinical presentation according to Hunt and Hess grade (HH) [12], initial radiological presentation according to computed tomography Fisher and/or modified Fisher scales [13] and/or, when available, the intraventricular haemorrhage (IVH) modified Graeb score [14].

Subgroup definition

For subgroup analysis, we identified studies with clinico-radiological definition of high risk of CVS and severe refractory CVS. High risk of CVS was defined as patients with Fisher scale >3 or modified Fisher scale >2 on initial brain computed tomography (CT) scan. Severe refractory CVS was defined as persistent or worsening deficits attributed to CVS, worsening of narrowing of intracranial arteries on digital subtracted angiography (DSA), or increased transcranial Doppler (TCD) velocities, despite best medical treatment, defined as standard of care for each study. Data were extracted from specific studies on these subgroups or from studies providing individual patient data. In these populations, we compared the following treatment groups: best medical treatment plus IA intervention (any pharmacological and/or any mechanical) versus best medical treatment alone.

Data analysis

A pooled estimate of unfavourable outcome rates was computed using a standard inverse-variance random-effect weighting method. Corresponding 99% confidence intervals (99% CIs) for single proportions were determined using the binomial theorem. Each study was assigned a weight according to the number of patients in that study. Heterogeneity between studies was reported using Cochrane $\chi 2$ (Cochrane Q) statistics and $I^2 = [(Q - df)/Q] \times 100\%$, where Q is the chi-squared statistic and df its degrees of freedom [15]. This describes the percentage of the variability that is due to heterogeneity rather than sampling error. According to the Cochrane handbook, heterogeneity was classified as moderate ($I^2 \geq 30\%$), substantial ($I^2 \geq 50\%$) or considerable ($I^2 \geq 75\%$) [16].

We assessed publication bias using scatter plots according to study size or precision, i.e. the "funnel plot" [17, 18]. We chose standard error for the vertical axis and the logit event rate, defined as logit (p) = log (p) − log (1 − p) where p is the event rate, for the horizontal axis [19, 20]. We assessed publication biases by means of visual analysis of funnel plots, as there is no validated statistical test to detect asymmetry, and used funnel plots and Egger's test in the subgroup comparisons [19]. The more pronounced the asymmetry, the more likely it is that the amount of bias will be substantial.

We assessed the relationship between outcome and subgroups of CVS (high risk of CVS and refractory/severe CVS), as well as location of the aneurysm and type of aneurysmal treatment (endovascular treatment vs surgical clipping).

We compared the outcome of the highest quality studies (19–28 points) with that of the others (i.e. 11–18 points). Publications were also compared according to the mid-year of the study (anterior or posterior to 2005, the median year of intervention among studies).

Due to the marked heterogeneity, uncontrolled nature of the data, and multiplicity of testing, a two-tailed P value of <0.01 was pre-specified to indicate statistical difference. All analyses were performed using Comprehensive MetaAnalysis 2.0 for Windows (Biostat, Englewood, NJ, USA).

Results

The initial search strategy yielded 1,130 papers from PubMed, 17 from the Cochrane Database of Systematic Reviews and 182 additional papers from EMBASE. Seven papers were obtained from other sources (please *see* ESM Fig. 1 for flowchart of studies selection).

After identification of duplicates, we assessed the eligibility of citations identified by the search strategy from titles and then from abstracts ($n = 278$). The final selection was made after reviewing full-text articles ($n = 95$) that either met the selection criteria or for which there was uncertainty regarding selection based on the abstract. We excluded 33 studies for the following reasons: outcome measures not provided ($n = 31$), duplicated populations ($n = 1$); methodological quality score <10 ($n = 1$).

Study characteristics

Sixty-two studies met all the inclusion criteria and were included in the analysis [21–81]. Table 1 describes their characteristics.

The mean value ± standard deviation (SD) of methodological quality score was 19.1 ± 4.2 and the median score was 20. None of the studies scored positively on all items. We identified 26 randomised trials [23, 24, 26, 28, 31, 44, 47, 49, 52, 53, 55–58, 65, 68, 73–77, 79–81]. A third of the studies (21 of 62) reported independent or blinded outcome assessment. The median year of publication was 2010 and the median year of treatment was 2005 (range, 1997–2013). Detailed characteristics included studies are displayed in ESM Table 1).

Baseline characteristics and subgroup analyses

Patient characteristics

We identified 62 studies (8,976 patients) including 26 randomised controlled trials (RCTs) [23, 24, 26, 28, 31, 44, 47, 49, 52, 53, 55–58, 65, 68, 73–77, 79–81]. Baseline clinico-radiological and demographic data are described in Table 2.

Of the 8,976 patients, 5,255 (59%) were females; the mean age was 50.1 years (SD, 4.92 years).

For CVS diagnosis (Table 2), DSA and TCD were used in, respectively, 49 studies (3,310 patients, 34%) and 39 studies (1,873 patients, 19%). A combination of TCD and DSA was used in 32 studies (3,027 patients, 31%) and CT angiography in 11 studies (1,351 patients, 1%).

The imaging modality used for delayed cerebral ischaemia (DCI) diagnosis was reported in 49/62 studies (non-contrast CT in 42 studies, 4,408 patients, magnetic resonance imaging [MRI] in seven studies, 296/8,976 patients, 3.3%).

The clinical outcome was clearly defined in 55 studies, assessed using the GOS or GOSE scales (37 studies, 5,976 patients), and mRs (31 studies, 4,056 patients). Contact was successfully made with authors to obtain the data for the remaining reports (7/7, 100%).

Subgroup characteristics

We identified 814 patients (15 studies) in the severe refractory CVS subgroup and 2,631 patients (ten studies) in the high-risk subgroup (*see* Table 2 for unfavourable outcome calculation).

Table 1 Characteristics of included studies

Variable	Value
Quality score	
Mean ± SD	19.1 ± 4.2
Range	10–27
10–14, *n* (%)	7 (11.5)
15–19, *n* (%)	22 (36.1)
20–24, *n* (%)	24 (39.3)
≥ 25, *n* (%)	8 (13.1)
Setting	
Multicentre	14 (21.3)
Single centre	48 (78.7)
Design	
ROT/RCT	26 (39.3)
Case–control/Case series/Others	36 (60.7)
Patient enrolment	
Prospective	41 (67.2)
Retrospective	20 (32.8)
Consecutive	18 (29.5)
Non-consecutive	43 (70.5)
Description of population	
Sources and methods of selection of participants	54 (87.1)
Baseline characteristics described	59 (95.2)
Outcome assessment	
Independent/blinded clinical outcome assessment	21 (34.4)
Outcome clearly defined	60 (98.4)
Evaluation of study limitations	
Imprecision and source of potential bias assessed	21 (33.9)
Selected patients for SAH grade or severity	46 (74.2)
Study objectives or pre-specified hypotheses	53 (85.5)

Values are expressed in absolute number of studies (percentage) unless otherwise specified

ROT randomised open label trial, *RCT* randomised control trial, *SAH* subarachnoid haemorrhage

Table 2 Characteristics of included patients

Patient characteristics	*n* patients (*n* studies)	Percent of all patients
Patients	8,976 (62)	-
Female gender	5,255 (56)	59%
Age, mean ± SD	50.1 ± 4.92	-
Aneurysm location		
Anterior	4,527 (56)	84%
Posterior	821 (56)	15%
Unknown/none	73 (54)	1%
Fisher grade		
1–2	1,256 (54)	19%
3–4	5,447 (54)	81%
Hunt and Hess grade		
1–3	3,429 (49)	80%
4–5	835 (49)	20%
Patient categories		
Unselected	5,367 (28)	60%
High risk	2,631 (10)	29%
Severe refractory	814(15)	10%
Diagnostic work-up method(s)		
Vasospasm:		
TCD	1,873 (39)	19%
DSA	3,310 (49)	34%
TCD & DSA	3,027 (32)	31%
CTA	1,351 (11)	14%
Perfusion CT	106 (4)	1%
Delayed cerebral: *Ischemia*		
CT	4,408 (42)	94%
MRI	296 (7)	6%
Treatment		
Endovascular	931 (18)	10.4%
No endovascular	5,175 (47)	57.6%
Endpoints		
mRs	4,056 (31)	45%
GOS/GOSE	5,976 (37)	66%

Values are expressed in absolute number of patients (studies) or a percentage, unless otherwise specified

SD standard deviation, *TCD* transcranial Doppler, *DSA* digital subtraction angiography, *CT* computed tomography, *CTA* CT angiography, *mRs* modified Rankin score, *GOS* Glasgow Outcome Scale, *GOSE* GOS Extended

Outcome

Overall, 2,490 of the 8,976 patients had an unfavourable outcome, including death (random-effect weighted average: 33.7%; 99% CI, 28.1–39.7%; Q value, 806.0; $I^2 = 92.7\%$). Publication bias is presented in the funnel plot analysis (Fig. 1).

Intervention efficacy in randomised trials

Intervention efficacy is illustrated in Fig. 2. The relative risk of unfavourable outcome was significantly lower in patients treated with Cilostazol compared with those treated without (R = 0.46; 95% CI, 0.25–0.85; $P = 0.001$; Q value, 1.5; $I^2 = 0$) (three studies, 259 patients). No other intervention produced a significantly different outcome.

Outcomes according to subgroup

A total of 978 patients in 21 studies corresponded to the definition of severe/refractory CVS. Seven of these studies (33%) where randomised trials. Of these, 431 patients had unfavourable outcome, including death (random-effect weighted average, 41.4%; 99% CI, 29.7–54.1%; Q value, 134.6; $I^2 = 85.1\%$). An unfavourable outcome occurred in 256 of the 761 patients in whom endovascular interventions

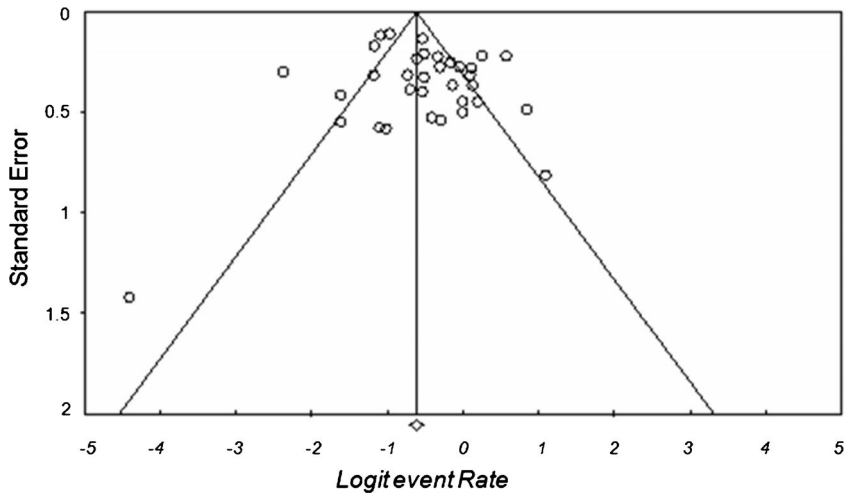

Fig. 1 Funnel plot of unfavourable outcome in cerebral vasospasm following aSAH. Funnel plot of unfavourable outcome in cerebral vasospasm following aSAH. Each *dot* represents a study; the *y*-axis represents the size of the study (e.g. number of subjects) and the *x*-axis shows the result of the study (e.g. the drug s measured average effect). Asymmetric funnel plot suggesting a relationship between treatment effect and study size

were performed, compared with 108 of the 217 patients without endovascular intervention in the same studies (RR = 0.68; 95% CI, 0.57–0.80; $P < 0.0001$; number needed to treat [NNT], 6.2; 95% CI, 4.3–11.2).

A total of 2,631 patients in 13 studies corresponded to the definition of high risk of CVS. Of these, 751 patients had an unfavourable outcome, including mortality (random-effect weighted average, 36.6%; 99% CI, 27.1–47.2%; Q value, 117.8; $I^2 = 89.8\%$).

No difference was found within the "high risk of CVS" subgroup in terms of unfavourable outcome when we compared patients in whom endovascular interventions were performed with patients without endovascular intervention.

Discussion

The main result of this systematic review is that, in cases of severe refractory cerebral vasospasm following aSAH, endovascular treatment, including intra-arterial injection of pharmacological agents or balloon angioplasty, may improve outcome compared with patients not treated using endovascular means.

To date, no randomised controlled trial of endovascular treatment in CVS following aSAH has been undertaken; therefore, clinical guidelines are based on case series [38, 82] and expert consensus.

From uncontrolled clinical series, there is evidence that both transluminal balloon angioplasty (TBA) and intra-arterial injection of pharmacological agents are beneficial in terms of immediate angiographic and short-term clinical outcomes [83]. Yet, no long-term clinical benefit has been demonstrated for endovascular approaches in CVS following aSAH (including IA injection of pharmacological agents and TBA), demonstrating our still limited understanding of DCI in aSAH patients. From a practical standpoint, TBA and IA pharmacological agents are most commonly used in combination, relying on the paradigm that TBA may effectively treat large-vessel/proximal CVS, allowing IA infusion of pharmacological agents to target CVS in the distal vasculature. Indeed, the discrepancy between clinical outcome and large-vessel CVS targeting [84] suggests that preventing/treating micro-vascular

Intervention (vs BMT)	N Studies	N Patients	Pooled Risk Ratio (99%CI) for UO	Risk Ratio (95% CI)	Q	p(Het)	I²	p(sig)
TBA	3	346		1.03 (0.82-1.28)	2.086	0.352	4.135	0.78
Cilostazol	3	259		0.46 (0.25-0.85)	1.479	0.477	0	**0.001**
Clazosentan	3	2127		0.88 (0.72-1.07)	3.04	0.22	34.11	0.09
MgSO4	6	574		0.82 (0.61-1.1)	1.802	0.876	0	0.08
Nicardipine	3	140		0.64 (0.15-2.79)	8.75	0.01	77.1	0.43
rtPA	3	139		0.83 (0.57-1.19)	0.16	0.92	0	0.18
SAS drainage	2	118		0.55 (0.2-1.52)	0	1	0	0.13
Statin	5	1239		1.08 (0.89-1.32)	5.452	0.363	8.283	0.31

Fig. 2 Pooled risk ratio in randomised studies. *BMT* best medical treatment, *CI* confidence interval, *$MgS0_4$* magnesium sulphate, *NNT* number of patients needed to treat to improve outcome in one patient, *p(Het) P* value associated to the Cochran χ2 statistical test for heterogeneity, *p(sig) P* value significance, *rtPA* tissue plasminogen activator, *SAS* subarachnoid spaces (includes cisternal and ventricular spaces), *TBA* transluminal balloon angioplasty

CVS is equally important to improve clinical outcome. Indeed, one of the putative limitations of proximal techniques such as TBA alone remains the inability to treat CVS affecting the distal cerebral vasculature, while targeting both proximal and distal vasculature may improve proximal flow and thus help deliver a therapeutically effective concentration and volume of vasodilators to the smaller distal cerebral microvasculature. Since the first description of mechanical dilation of intracranial vessels [85], over-the-wire balloon techniques for intracranial angioplasty have developed considerably. The current thinking is that transluminal balloon angioplasty acts by stretching the vessel wall, leading to morphological and functional changes in the smooth muscle fibres, resulting in impairment of contractility. At a cellular level, it has been shown that there is fragmentation of the collagen matrix and flattening of the endothelial cells, resulting in permanent restoration of vessel diameter. This has been demonstrated to be durable in both canine and primate models [86]. On the other hand, the infusion of directly acting vasodilatators such as verapamil have demonstrated to be effective in improving both vessel calibre and short-term clinical outcome [38], but similarly failed to demonstrate improved long-term outcomes. Further, the only randomised trial comparing intra-arterial nimodipine and balloon angioplasty versus intra-arterial nimodipine alone did not demonstrate that a clinical benefit derived from this approach [83]. Notably, only one RCT compared prophylactic transluminal balloon angioplasty versus no prophylactic treatment within 96 h of aneurysm rupture [81]. Patients undergoing prophylactic transluminal balloon angioplasty experienced a non-significant reduction in delayed cerebral ischaemia incidence. A significant decrease in therapeutic angioplasty was observed, however, in patients who had prophylactic angioplasty compared with controls, but no long-term difference in clinical outcome was demonstrated. Our study suggests a long-term clinical benefit from endovascular approach in the context of severe/refractory CVS following aSAH and in addition to best available medical treatment. Given the lower level of evidence from which our pooled results derive, larger multicentre prospective randomised trials are necessary to confirm these results. To elucidate the most efficient therapeutic approaches for the treatment of CVS following aSAH, pragmatically designed trials assessing the efficacy of TBA alone or in combination with direct-acting vasodilators of different pharmacological actions are needed.

Another interesting result is the finding that in patients treated with Cilostazol the rate of unfavourable outcome was significantly lower when compared to those not receiving Cilostazol. This result, in line with a previously published meta-analysis of RCTs and 'quasi randomised' trials [87], provides further evidence for future trials using Cilostazol, and is an incentive for investigating other phosphodiesterase 3 inhibitors such as Milrinone in randomised trials targeting CVS. A recent study, with a case–control design, has demonstrated that Cilostazol "remarkably" improved outcome after aSAH [88], with an even more pronounced effect on CVS incidence. Phosphodiesterase 3 inhibitors were initially developed for their inotropic function in the treatment of cardiogenic shock. The precise mechanism by which they affect outcome in aSAH patients is not yet fully elucidated, but part of it is carried by their vasodilator effect and hence improvement of cerebral perfusion in CVS patients. Cilostazol has notably shown to decrease middle cerebral arteries flow velocities in healthy patients, suggesting a direct vasodilatation effect, even on larger vessels [89]. Moreover, in experimental studies, Cilostazol has demonstrated pleiotropic effects, including NO production, endothelial damage and smooth muscular cell proliferation prevention, as well as an antiplatelet function [89]. The combination of these effects suggests that Cilostazol targets both large and small vessel CVS, and may influence the formation of microthrombi in the distal vasculature. This may explain the translation to better clinical outcomes in aSAH patients, although confirmation from randomised trials is lacking.

Several limitations may have affected our results. First and foremost, there is a significant level of heterogeneity amongst the included studies. Given this, one may question the initial decision to proceed with a meta-analysis with a risk of giving credibility to wrong results, since selected populations are variable and clinical settings diverse. We aimed at overcoming this drawback by classifying patients according to their initial clinico-radiological evaluation in each study, to be able to analyse outcomes according to vasospasm risk, presence or severity as well as the severity of the clinical presentation. Nevertheless, data presentation was not uniform among source papers and we were unable in the majority of them to assess some important aspects of the patients care that may significantly influence the results of this work. Most notably, there was an important heterogeneity in the reporting of baseline prophylactic measures for CVS. In the absence of high-level evidence-established standards, it has been shown that there is a considerable variation in individual neuro-critical care units procedures for the investigation and management of CVS in aSAH patients [90].

In contrast with previous systematic reviews [4, 5], we only included studies and randomised trials with endpoints including clinical outcome, allowing us to use an easily assessed and homogenous endpoint. Conversely, we acknowledge that the definition and investigation of CVS varied in each individual study, and the variety of the approaches precluded to further adjust our analyses for this parameter. Furthermore, while we used random effects models, the important heterogeneity in study quality and, notably, the pooling of results from randomised trials and observational studies represent a significant limitation to the interpretation of our results. Of note, we also decided to include only studies published since 2006. Our justifications include the recent publication of many

international trials, technical and procedural advances in endovascular procedures, and a literature that is less likely to be exploitable as we go back in time, when standards of reporting observational studies were either not available or rarely implemented. Indeed, compared with previous systematic reviews [4, 5], there seems to be some improvement in methodological quality, with a median methodological score of 20.

Finally, we also acknowledge that some publications might have been missed since we included only publications in English or French. This may lead to a language bias, as studies with statistically significant results are known to be more likely to be published in English [91].

To conclude, this systemic analysis showed an unfavourable outcome in one-third of patients treated for cerebral vasospasm following aSAH. Cilostazol is the only pharmacological intervention associated with a lower unfavourable outcome rate. The relative risk of unfavourable outcome was significantly lowered in severe refractory CVS patients in whom endovascular interventions (including pharmacological and/or balloon angioplasty) were performed. In light of these results, the most rational and ethical approach to patient care would be to design a randomised trial comparing endovascular treatment to best medical treatment in severe refractory CVS.

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Methodology: systematic review and meta-analysis.

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