Comparison of Blister Aneurysm Treatment Techniques: A Systematic Review and Meta-Analysis

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Abstract

Objective: Blood blister aneurysms are small, thin-walled, rapidly growing side-wall aneurysms that have proven particularly difficult to treat, and evidence-based guidance for treatment strategies is lacking. A systematic review and meta-analysis was performed to aggregate the available data and compare the three primary treatment modalities.

Methods: We performed a comprehensive literature search according to PRISMA guidelines followed by an indirect meta-analysis that compares the safety and efficacy of surgical, flow-diverting stents (FDS), and other endovascular approaches for the treatment of ruptured blood blister aneurysms.

Results: A total of 102 studies were included for quantitative synthesis with sample sizes of 687 treated surgically, 704 treated endovascularly without FDS, and 125 treated via flow-diversion. Comparatively, FDS achieved significantly reduced rates of perioperative retreatment compared to both surgical (P=0.025) and non-FDS endovascular (P<0.001). The FDS subgroup also achieved a significantly lower incidence of perioperative rebleed (P<0.001), perioperative hydrocephalus (P=0.012), postoperative infarction (P=0.002), postoperative hydrocephalus (P<0.001), and postoperative vasospasm (P=0.002) when compared to those patients in the open surgical subgroup. While no significant differences were found between groups on the basis of functional outcomes, angiographic outcomes detailed by rates of radiographic complete occlusion were highest for surgical (90.7%, 262/289) and FDS (89.1%, 98/110) subgroups versus the non-FDS endovascular subgroup at (82.7%, 268/324).

Conclusion: Flow-diversion appears to be an effective treatment strategy for ruptured BBAs with lower rates of perioperative complications when compared to surgical and other endovascular techniques but studies investigating long-term outcomes following flow-diversion warrant further study.

Introduction

Blood blister aneurysms (BBAs), as initially described by Takahashi et al., represent a rare but surgically challenging vascular pathology arising from non-branched arteries.[1,2] Although often reported as occurring in the anterior or posterior circulation, most BBAs characteristically present at the supraclinoid segment of the ICA but can occur in other intracranial vessels as well.[3] They are particularly rare, accounting for approximately 0.3 – 1% of all intracranial aneurysms and 6.6% of ruptured intracranial aneurysms.[4,5] Patients classically present with an acute subarachnoid hemorrhage (SAH), rapidly evolving clinical course and angiographic imaging demonstrating a small broad-based intracranial arterial wall irregularity. Although pathophysiologically obscure, ruptured BBAs are thought to represent an underlying intracranial arterial dissection and are associated with a high degree of vessel wall fragility and prone to growth and re-rupture.[6-9]

BBAs present a therapeutic challenge because of their difficulty to treat by conventional surgical reconstruction and high susceptibility to intra-operative rupture as well as rebleed postoperatively.[4] There are many treatment modalities in clinical use for the treatment of BBAs. Patients may be treated surgically by direct clipping, wrapping, trapping with or without bypass, artery occlusion or by endovascular approaches via coils, stent-assisted coiling, multiple overlapping stents or with flow-diverting stents. While various techniques are used to secure these difficult lesions, no one treatment modality has proven distinctly superior in the literature. Recently, reports of flow-diverting stents used in BBAs have been coupled to lower morbidity and mortality compared to more invasive surgical techniques.[10-15]

This systematic review and meta-analysis aims to analyze the growing body of literature reporting outcomes of flow-diverting stents used in the management of BBAs compared to conventional treatment approaches. The clinical indications, outcomes, and potential complications of these procedures are reviewed.

Methods

Literature Search

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] A literature search was conducted using the key words "blister aneurysm" entered for search in electronic databases PubMed, Cochrane Central Register of Controlled Trials, and Scopus from dates of their inception to May 2020. In addition, ClinicalTrials.gov was used for access to grey literature. Our electronic search strategy is presented and follows the 2009 PRISMA Group guidelines outlined in Supplemental Figure 1. Identified studies were uploaded into Endnote and duplicates were removed.

Study Selection

Pre-specified inclusion and exclusion criteria were defined a priori. Studies were eligible for inclusion if they met the following criteria: 1) adult patients (18 or older); 2) English language; 3) available data on ruptured blister aneurysms treated by surgery and/or endovascular; 4) adequate data on clinical and/or angiographic outcomes; 5) studies that were retrospective or prospective with at least one patient. Abstracts, conference presentations, editorials, and animal studies were excluded. Review articles and meta-analyses were also excluded.

Two authors (A.S.H. and J.N.J.) independently screened the titles and abstracts of all articles based on the pre-specified inclusion and exclusion criteria. Articles that met the inclusion criteria were then full-text reviewed independently by (V.S., S.R., and A.O.) and eligible articles were selected based on the set criteria. Discrepancies between the authors were resolved by involvement of other authors (A.S.H., J.N.J.). References of relevant articles were also reviewed to ensure no studies were neglected in our electronic search.

Data Extraction

Data were independently extracted by two authors (V.S. and S.R.) using a standardized form, and any disagreement was resolved by consensus. Data were independently confirmed by two other authors (A.S.H and J.N.J). The study design, data extraction, results review, and reporting were overseen by the senior investigator (J.N.J).

For each study evaluated, the following data were extracted: study design, patient demographics, comorbidities, presenting clinical status (Hunt and Hess or Fisher grades), aneurysm details (location and size), treatments (clipping and suturing, parent artery occlusion, trapping, wrapping, coil embolization, flow-diverting stent, stent placement alone, stent-assisted coiling, multi-stent overlapping), anti-platelet therapy, complications, outcomes (perioperative mortality or morbidity, early and late angiographic outcomes, clinical outcomes measured by modified Rankin Scale (mRS), postoperative complications, and survival status). Good outcome was defined as an mRS score of 0-2 and poor outcome as mRS score 3-5. For studies in which quantitative measures were not available, favorable neurologic outcome was dependent on terms such "good recovery". Distinctions between perioperative and postoperative outcomes were defaulted to two weeks after surgery unless otherwise stated by each individual study.

Outcome Measures

Clinical outcomes were extracted for the overall population of patients diagnosed and treated for ruptured blood blister aneurysms. The primary outcome of interest was to perform analyses comparing the clinical outcomes of patients treated with a flow-diverting stents versus surgery and all other endovascular treatments.

Statistical Analysis

An indirect meta-analysis was performed comparing the outcomes of interest of the three groups. This analyzes each arm separately with their corresponding subgroup pooled result and compares all three results. For any statistically significant comparison, post-hoc analysis was conducted for individual comparisons between the arms. Any study treatment group with a sample size less than 3 was excluded due to limited power of that study. Results were represented by average proportion (effect size, ES) with their corresponding 95% confidence intervals (CIs). Results were also depicted as forest plots, and heterogeneity between groups indicates statistical significance for all groups' differences. Statistical analysis was performed using STATA 16 (Stata-Corp 2019. STATA Statistical Software: Release 16. College Station, TX: StataCorp LP). P-values <0.05 were considered statistically significant.

Assessing Risk of Bias of Studies and Results

Risk of Bias assessment for quality of evidence of analyzed results was conducted using Grading of Recommendations, Assessment, Development and Evaluations (GRADE), whereby results are assessed based on inconsistency, indirectness, imprecision, and other considerations. [17] Risk of bias assessment for individual studies was conducted using the modified Newcastle-

Ottawa Scale (NOS), whereby “Comparability of Cohorts” was removed in our assessment due to the nature of indirect meta-analysis depicted in Supplemental Tables 1 and 2.[18]

Results

Study selection.

The initial literature search identified 762 studies using PubMed, Scopus, Cochrane, and Clinicaltrials.gov (Supplemental Figure 1). After duplicates were removed, 440 articles were left for review. An additional 61 records were removed at this stage via thorough inspection reaching a total of 379 results. Overall, 191 studies met inclusion and exclusion criteria, were full-text reviewed, and data were compiled for qualitative synthesis. For meta-analysis, pre-specified eligibility required at least 3 patients per treatment group with adequate reports of angiographic outcome, leaving a total of 102 studies for quantitative synthesis.

Patient Demographics and Clinical Characteristics for Qualitative Synthesis.

For qualitative synthesis, 1845 patients from 191 studies were included. The median average patient age was 50 years, while the median average percentage of female patients was 72.15% (Table 1). BBA location was provided in 184 of 191 studies and 93.75% (1755/1872) were found along the ICA, whereas 1.60% (30/1872) and 1.50% (28/1872) were localized to the middle cerebral and basilar arteries, respectively (Table 1). HH scores were reported for 97 of 191 studies and of such, 10.75% (128/1191), 44.67% (532/1191), 27.54% (328/1191), 13.60% (162/1191), and 3.44% (41/1191) of patients presented with HH scores of I, II, III, IV, and V, respectively (Table 1).

Quantitative Synthesis Outcomes Summary.

Collectively, the perioperative mortality rate was 7.4% (103/1396) and 232 procedural complications were identified. Perioperative rebleeding was reported in 225 cases (20.11%) and 118 patients (13.53%) were retreated in the perioperative setting. Overall, short-term occlusion rate and mRS values were inconsistently reported. Findings in the postoperative setting identified a complete occlusion rate of 65.11% (334/513) and a follow-up (FU) mRS of 0-2 in 86.8% (729/840) of patients. Postoperative complication rates including aneurysm regrowth and rebleeding were 10.56% and 5.62%, respectively. Overall, the postoperative mortality rate was 5.3% (69/1313). Data is summarized in Table 2.

Analysis of BBA Treatment Groups.

Open Surgery. There were 53 studies with 687 patients treated with open surgery. The majority of surgical interventions involved clipping, a combination of clip and wrapping, or trapping and EC-IC bypass. Of the 35 studies providing data for procedural complications, the rate was 45.6% (177 of 388 patients), with the most common complications being intraoperative severe vasospasm and rebleed. Perioperative mortality occurred in 57 of 592 patients (9.6%). Perioperative complication rates including retreatment, vasospasm, and rebleeding were 13.5% (49 of 363), 24.6% (80 of 325), and 30.8% (184 of 597), respectively, as well as ischemic stroke (15.2%, 44 of 290), and hydrocephalus (38.4%, 66 of 172). Parent artery stenosis was reported in 43 of the 290 patients (14.8%). Postoperative vasospasm and rebleed were found in 25.7% and 8.4% of cases, respectively. Complete occlusion was found in 262 of 289 (90.7%), while the remaining 27 patients obtained either near complete or incomplete occlusion at follow-up. Of 350 patients, 281 (80.3%) were reported as achieving good mRS scores (mRS 0-2) at follow-up. Postoperatively, mortality occurred in 50 of 567 (8.8%) patients. All results provided are summarized in Table 2.

Non-FDS Endovascular. There were 42 studies with 704 patients treated endovascularly without the use of flow-diverting stents. Several of the procedural techniques used included stenting with or without coiling, stent-in-stent placements, and embolization. Among 29 studies, there was a procedural complication rate of 14.2% (44 of 310 patients). Perioperative complication rates of early retreatment, vasospasm, rebleeding were (16.4%, 64/390), (24.6%, 79/321), and (9.2%, 38/414) as follows. Stenosis of the parent artery was found in 13 of 182 patients (7.1%). The perioperative mortality rate was 5.9% (40 of 679). Postoperatively, patient mortality was documented in 19 of 627 patients (3.0%). Postoperative rebleeding was found in 14 of 371 (3.8%) and postoperative infarction occurred in 16 of 292 (5.5%). Complete occlusion was achieved postoperatively in 219 of 373 cases (58.7%), and at latest follow-up this number increased to 82.7%. Upon follow-up, 348 of 379 (91.8%) patients achieved a good mRS score (0-2), while 31 were reported to have poor mRS scores. All results provided are summarized in Table 2.

Flow-Diversion. There were 18 studies with 125 patients treated endovascularly with flow diverting stents. We identified a procedural complication rate of 9.9% (11 of 111 patients), a perioperative mortality rate of 4.8% (6 of 125), perioperative complication rates including retreatment, vasospasm, rebleeding were 4.2%, 8.3%, and 2.8% respectively. Arterial stenosis was found in 7 of 69 patients (10.1%). In the postoperative setting, patient mortality was documented in 0 of 119 patients. While perioperative occlusion and mRS were not frequently reported, in the postoperative and follow-up studies, 100 of 111 (90.1%) patients maintained a good mRS (0-2) and the remaining 9.9% of patients fell between mRS scores of 3 to 5. At most recent radiographic follow-up, complete angiographic occlusion was found in 98 of 110 (89.1%), while 12 patients obtained either near complete (3/110) or incomplete occlusion (9/110).

Regrowth was found in 3 of 108 cases (2.8%). Postoperative rebleeding was reported in 0 of 103 patients while postoperative infarction occurred in 2 of 79 patients (2.5%). All results provided are summarized in Table 2.

Comparative outcome variables.

Perioperative Rebleeds. A total of 1119 patients were included in this analysis. Overall effect size between the procedural techniques was 0.13 (95% CI: 0.09-0.18) and indicated statistically significant difference between the arms (p<0.001). Post-hoc analysis indicated that patients who underwent open surgery had higher average proportion of perioperative rebleeds compared to those who underwent FDS [0.26 (0.18-0.34) vs. 0.00 (0.00-0.03); p=0.011]. Those who underwent FDS had lower perioperative rebleed rates compared to those who underwent non-FDS endovascular treatment [0.00 (0.00-0.03) vs. 0.05 (0.02-0.09); p=0.049].

Perioperative Retreatments. A total of 872 patients were included in this analysis. Overall effect size between the procedural techniques was 0.10 (95% CI: 0.06-0.14) and indicated statistically significant difference between the three techniques (p<0.001). Post-hoc analysis indicated that patients who underwent open surgery had higher average proportion of perioperative retreatment compared to those who underwent FDS [0.10 (0.04-0.16) vs. 0.01 (0.00-0.05), respectively; p=0.025]. Those who underwent FDS had lower rates of the outcome compared to those who underwent non-FDS endovascular treatment [0.01 (0.00-0.05) vs. 0.16 (0.09-0.23), respectively; p<0.001]. All previous results are depicted as forest plots in Figure 1.

Postoperative Infarction. A total of 750 patients were included in this analysis. Overall effect size between the procedural techniques was 0.06 (95% CI: 0.03-0.10) and indicated statistically significant difference between the three techniques (p=0.001). Post-hoc analysis indicated that patients who underwent open surgery had higher average proportion of postoperative infarction compared to those who underwent FDS [0.15 (0.08-0.23) vs. 0.00 (0.00-0.04), respectively; p=0.002]. Those who underwent FDS had similar rates of the outcome compared to those who underwent non-FDS endovascular treatment [0.00 (0.00-0.04) vs. 0.01 (0.00-0.03), respectively; p=0.682].

Complete Occlusion at Last Follow-up. A total of 723 patients were included in this analysis. Overall effect size between the procedural techniques was 0.86 (95% CI: 0.81-0.91) and indicated statistically significant difference between the three techniques (p=0.034). Post-hoc analysis indicated that patients who underwent open surgery had similar average proportion of complete occlusion at last follow-up compared to those who underwent FDS [0.93 (0.86-0.98) vs. 0.85 (0.75-0.94), respectively; p=0.138]. Those who underwent FDS had similar rates of the outcome compared to those who underwent non-FDS endovascular treatment [0.85 (0.75-0.94) vs. 0.79 (0.70-0.87), respectively; p=0.385]. All previous results are depicted as forest plots in Figure 2.

Risk of Bias of Studies and Results.

According to the GRADE assessment, outcomes ranged from very low to moderate certainty on our evidence. Some outcomes contained variable 95% CIs, resulting in imprecision. Other studies may have inconsistent number of studies for each group, resulting in inconsistency for those outcomes. GRADE assessment is shown in Supplemental Table 1. According to the modified NOS, scores for studies ranged from 4 to 6. The two categories that were non-satisfactory for some of the studies were inadequate follow-up duration and outcome of interest. Some studies failed to define final follow-up while others included patients who were reoperated.

However, those patients were excluded in our analysis. NOS scoring is shown in Supplemental Table 2.

Additionally, it is important to note that angiographic diagnosis of a blood blister aneurysm has its challenges which may lead to inconsistencies between sites[19,20]. The utility of conventional CTA in characterizing the morphology that defines a BBA is poor and although most BBAs are detected with digital subtraction angiography and 3D rotational angiography, some are unidentifiable pre-procedurally[21-23]. Hence, discriminating between BBAs and other aneurysms may be at risk of bias across studies performing either endovascular or surgical repairs. This may confound results due to the inherent limitations in operative views that exist between each modality and its ability to identify an aneurysm as a blood blister with and without direct visualization. Future improvements in imaging techniques will likely enhance the preoperative detection and morphological classification of these lesions.

Discussion

Our meta-analysis combined outcome data of 102 studies to assess the safety and efficacy of the various techniques used in the treatment of acutely ruptured BBAs. Specifically, we aimed to compare the efficacy of open surgical techniques and other endovascular modalities to flow-diversion. Our findings suggest that FDS are efficacious in treating BBAs with findings that suggest lower rates of perioperative rebleeds, retreatments, hydrocephalus, and vasospasm.

The classical presentation of a patient with a BBA is a severe SAH and in our quantitative synthesis most patients presented with an HH grade II and III at 44.3% and 29.0%, respectively. Unfortunately, BBA diagnoses can often be delayed at the time of presentation because CTA is less sensitive in diagnosing small aneurysms or those localized near the skull base.[24] Nevertheless, these aneurysms do necessitate early intervention as the risk of enlargement and re-rupture increases as treatment is delayed.[24] In terms of morphology, these aneurysms are small, thin-walled, half dome-shaped bulges with a broad neck that typically occur at non-branching portions of the parent vessel. They are fragile and technically challenging to treat. Currently, there is no consensus on a single recommended treatment approach and a search of the literature reveals no randomized controlled trials on the topic to date. Hence, our study aims to add to the growing body of literature on how flow-diverting techniques compare to other described approaches for the management of these challenging lesions.

Our study found that BBAs treated with flow-diverting stents achieved a lower overall retreatment rate when compared to open surgical and other endovascular techniques. Specifically, the rates of retreatment were as follows: FDS (4.2%, 5/119), open surgical (13.5%, 49 of 363), and other endovascular (16.4% (64/390). The difference in retreatment achieved significance for FDS versus open surgery (P = 0.025) and FDS versus other endovascular techniques (P <0.001). Our data comparing flow-diversion against other endovascular techniques are consistent with previously published reports. For example, Rouchaud et al. compared the outcomes of patients treated with FDS to those treated with reconstructive endovascular techniques such as stent-assisted coiling and also found a lower rate of retreatment among those in the FDS treatment group, (6.6% versus 27.1%, P = 0.0002).[25] Our findings were also similar to the literature in comparing endovascular techniques to open surgery in that although surgery achieves superior rates of obliteration, it does carry a higher risk of rupture and other complications.[26,27] Endovascular techniques, on the other hand, carry a lower risk of rupture with comparable neurological outcomes, but our findings demonstrate higher rates of retreatment among this subgroup 16.4% versus 13.5%.[28 26] These findings are also corroborated by a systematic review by Szmuda et al. where clipping was associated with higher rates of intraoperative rupture (OR 6.5; 95% CI 1.2 to 34.3), whereas stent-assisted coiling increased the likelihood of retreatment (OR 4.1; 95% CI 1.3 to 13.1) and incomplete occlusion (OR 2.6; 95% CI 1.0 to 6.6).[29] Similar findings were observed in a study by Ricciardi et al. which found higher rates of perioperative mortality in the surgical subgroup at 7.4% compared to those treated endovascularly at 2.8%.[30] They also found a higher mean mRS (3.6 versus 2.5) and a significantly higher complication rate among those treated surgically.[30] Our study adds to the current understanding by implementing a comparison of FDS to these other traditionally used approaches, which has yet to be explored in the literature.

The subgroup treated by FDS achieved significantly lower rates of perioperative rebleeds compared to those treated surgically (2.8%, 3/108 vs 30.8%, 184 of 597; P <0.001) but did not reach significance when compared to other endovascular approaches (2.8%, 3/108 vs 9.2% 38/414; P = 0.053). In a systematic review of 63 studies, Gonzalez and colleagues compared the outcomes of BBAs treated surgically or endovascularly.[26] They found that rebleeding occurred in 12.5% of cases treated with stent-assisted coiling, whereas the overall perioperative rate of rebleed for those treated surgically was 30%.[25] In addition, Rouchaud et al. reported a rebleed rate of 8.3% in cases treated endovascularly, and that rate varied between deconstructive (11%, 95% CI 0.9 to 21.2) and reconstructive (8%, 95% CI 4.6 to 11.4) endovascular techniques.[25] Rouchaud et al. had relatively few FD cases but also reported lower rates of rebleed for flow-diverter reconstructive techniques (6.5%, 95% CI 0 to 12.8) versus non-flow-diverter reconstructive approaches (8.7%, 95% CI 4.6 to 12.8) although this did not reach significance (P = 0.06).[25]

Although flow-diverting stents achieved lower rates of rebleed above, it is important to consider antiaggregant management which balances risks of acute hemorrhagic complications with risks of thromboembolic events. The pipeline embolization devices (PED) used in flow diversion are unique in that they confer a 3-to-5-fold increase in surface area compared to conventional intracranial stents.[31] These devices are composed of 75% cobalt/chromium and 25% platinum/tungsten which acts as a nidus for platelet aggregation, and therefore necessitates the use of dual antiplatelet therapy.[31] Gupta and colleagues disseminated a survey to neurosurgeons at academic cerebrovascular centers to assess the dual antiplatelet regimen used following PED placement and 100% of respondents reported using clopidogrel and aspirin as first-line agents.[32] It was consistently found across studies, that clopidogrel hypo- or non-responsiveness was followed with administration of aspirin/ticagrelor or aspirin/prasugrel. According to a multicenter cohort study by Adeeb et al. clopidogrel non-responders were at significantly higher risk of a thromboembolic event compared to responders at 17.4% versus 5.6%, respectively.[33] And despite data that half of patients show some degree of clopidogrel resistance, platelet function testing (PFT) remains controversial and is not uniformly performed.[34,32,33] Overall, the antiplatelet regimens for intracranial aneurysms treated with flow diversion is yet to reach standard protocols across sites but use of PFT and assessment of ticagrelor efficacy, now preferred over clopidogrel by the AHA, warrant further investigation.[35]

The surgical subgroup achieved the highest rate of postoperative complete occlusion (96.3%, 105/109), whereas flow-diversion and other endovascular techniques obtained markedly lower rates at (32.3%, 10/31) and (58.7%, 219/373), respectively. Poorer immediate occlusion rates are expected of flow-diverting stents as there is rarely immediate complete occlusion, but the low re-rupture rates imply that the flow diversion effect is largely protective against re-rupture. Because FDS devices both divert flow and are scaffolds for neointimal proliferation, complete radiographic occlusion is often not observed until endothelialization has occurred. The time course for radiographic obliteration following FDS is thought to be variable and dependent on individual aneurysm morphology.[36] Notably, at post-hospitalization imaging follow-up, rates of complete occlusion for the FDS subgroup markedly increased to 89.1% (98/110). Complete occlusion remained high for the surgical group (90.7%, 262/289) when compared to that of the non-FD endovascular group (82.7%, 268/324). In a study by Scerrati et al. they found that coiling conferred a higher rate of immediate complete occlusion at 63.4% compared to flow-diversion at 53.7%, but a comparable occlusion rate was reported at follow up.[37] In a meta-analysis by Peschillo et al., nearly all patients who underwent open surgery achieved early complete occlusion (96.4%), whereas only 44.5% of patients who underwent endovascular treatments reached postoperative complete occlusion.[38] In a meta-analysis of 31 studies examining reconstructive and deconstructive endovascular techniques, the immediate postoperative occlusion rate was 40.6% and increased to 72.8% overall on follow-up.[25] Deconstructive techniques achieved higher rates of early complete occlusion compared to reconstructive techniques (77.3% versus 33%, P = .0003).[25] Interestingly, within the reconstructive group, the FDS subgroup achieved greater long-term complete occlusion at follow-up compared to those treated with other reconstructive endovascular techniques (90.8% versus 69.7%, P=0.005).[25] These results align with the outcomes concluded in our study where flow-diversion trended towards being superior to other endovascular approaches on the basis of angiographic outcomes at follow-up with 89.1% versus 82.7%, respectively.

Strengths and limitations.

The detailed literature search spanned several databases, and studies underwent assessment by multiple reviewers. While our study searched a large volume of literature, it also includes decades of clinical management which makes standardization between treatment groups particularly challenging. The inclusion of older data may introduce some confounders because these patients were more likely treated with open approaches while the benefits of modern ICU care were lacking. In addition, there are published data to suggest that outcomes following a SAH have improved over time and are likely due to optimizing ICU care along with the advancement of endovascular techniques.[39,40] Inconsistent reporting of antiaggregant therapy across studies compromised our ability to meta-analyze these data which represents an important reporting bias since antiplatelet therapy is crucial for certain treatments. Small sample sizes for the FDS group, in particular, make it difficult to draw statistically significant differences between groups. However, this meta-analysis is the first to directly compare the safety and efficacy of FDS to both surgical and other endovascular approaches.

Conclusions.

Overall, our findings summarize the data of 102 studies and therefore serves as a clinically useful tool to estimate treatment effects and outcomes for BBAs. Flow-diversion is a promising endovascular technique for treating blood blister aneurysms. Flow-diversion offers lower rates of perioperative complications when compared to other frequently used treatment techniques and demonstrates comparable morbidity, mortality and functional outcomes. Studies assessing long-term outcomes following flow-diversion for the treatment of blister aneurysms are needed.

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Figure legends

Figure 1. Meta-analysis shows comparison of perioperative outcomes for each treatment group. The effect size (ES) for each group is represented by a diamond and provided numerically with its corresponding 95% CI. Overall P-values were calculated for each outcome. When heterogeneity between groups reached significance, P-values for each treatment subgroup are given with respect to FDS subgroup comparison. FDS indicates flow-diverting stents.

Figure 2. Meta-analysis shows comparison of postoperative outcomes for each treatment group. The effect size (ES) for each group is represented by a diamond and provided numerically with its corresponding 95% CI. Overall P-values were calculated for each outcome.

When heterogeneity between groups reached significance, P-values for each treatment subgroup are given with respect to FDS subgroup comparison. FDS indicates flow-diverting stents.

Supplemental Materials:

Supplemental Figure 1 (Prisma Flow Diagram)

Supplemental Table 1 (Risk of bias assessment GRADE)

Supplemental Table 2 (Newcastle-Ottawa Scale)

Comparison of Blister Aneurysm Treatment Techniques: A Systematic Review and Meta-Analysis

Table 1 Qualitative synthesis patient characteristics

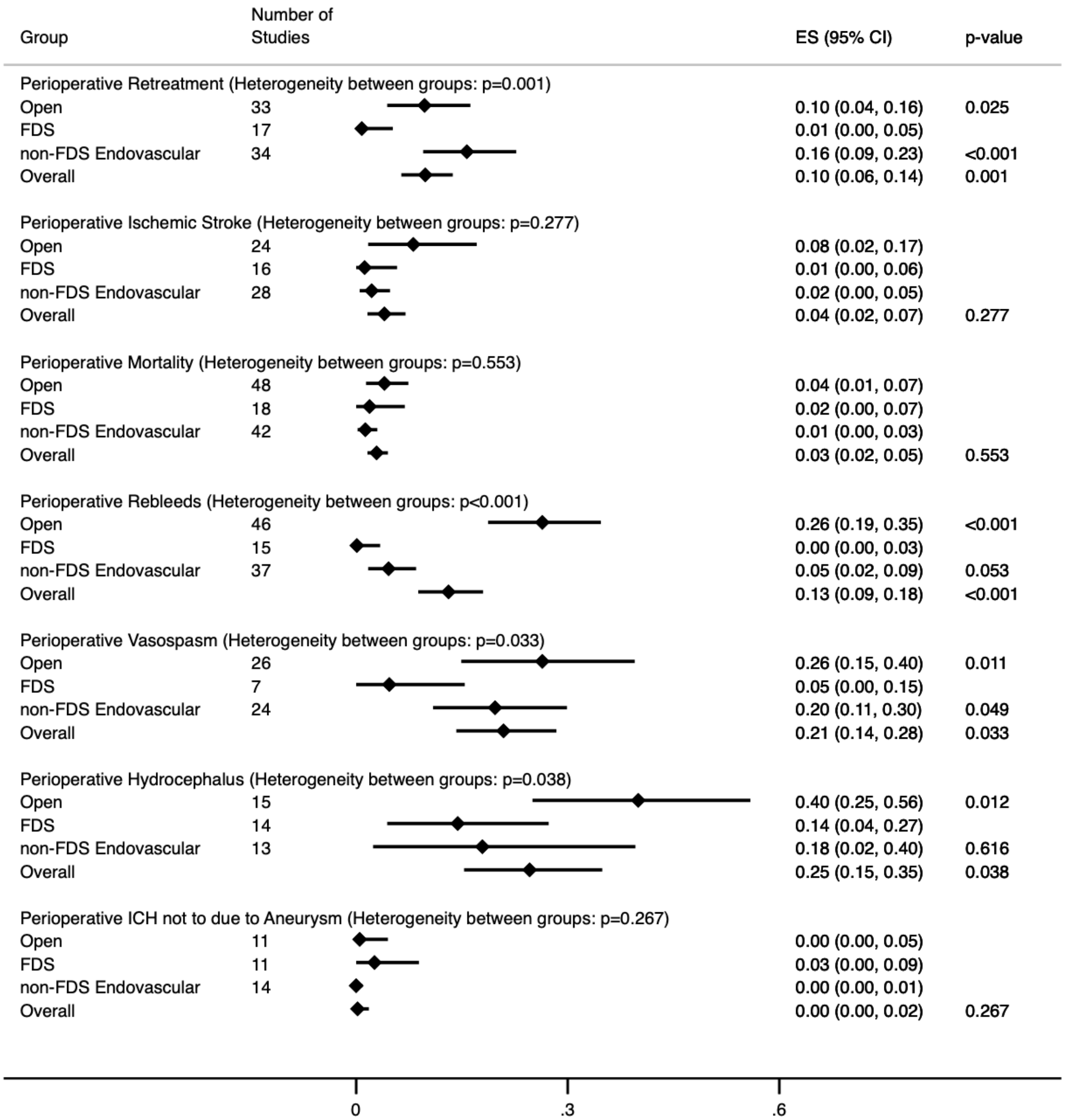
Characteristics	
Age (years)	
Median average age	50
Sex	
Median % female	72.15 %
Aneurysm location	
Internal carotid artery	93.75 %
Middle cerebral artery	1.60 %
Basilar artery	1.50 %
Anterior communicating artery	1.01 %
Anterior cerebral artery	0.80 %
Posterior cerebral artery	0.75 %
Posterior communicating artery	0.27 %
Vertebral artery	0.16 %
Posterior inferior cerebellar artery	0.16 %
Hunt and Hess grade	
I	10.75 %
II	44.67 %
III	27.54 %
IV	13.60 %
V	3.44 %

Table 2 Chief morbidity and mortality outcomes sub-divided by treatment group

Number of events / patients				
Outcome	**Overall (%)**	**Open (%)**	**FDS (%)**	**Endo (%)**
Perioperative Rebleed	225/1119 (20.1)	184/597 (30.8)	3/108 (2.7)	38/414 (9.2)
Perioperative Retreatment	118/872 (13.5)	49/363 (13.5)	5/119 (4.2)	64/390 (16.4)
Perioperative Mortality	103/1396 (7.4)	57/592 (9.6)	6/125 (4.8)	40/679 (5.9)
Postoperative Rebleed	52/926 (5.6)	38/452 (8.4)	0/103 (0.0)	14/371 (3.8)
Postoperative Regrowth	112/1061 (10.6)	20/290 (6.9)	3/108 (2.8)	89/663 (13.4)
Postoperative Mortality	69/1313 (5.3)	50/567 (8.8)	0/119 (0.0)	19/627 (3.0)
Postoperative Complete Occlusion	334/513 (65.1)	105/109 (96.3)	10/31(32.3)	219/373 (58.7)
FU Complete Occlusion	628/723 (86.9)	262/289 (90.7)	98/110 (89.1)	268/324 (82.7)

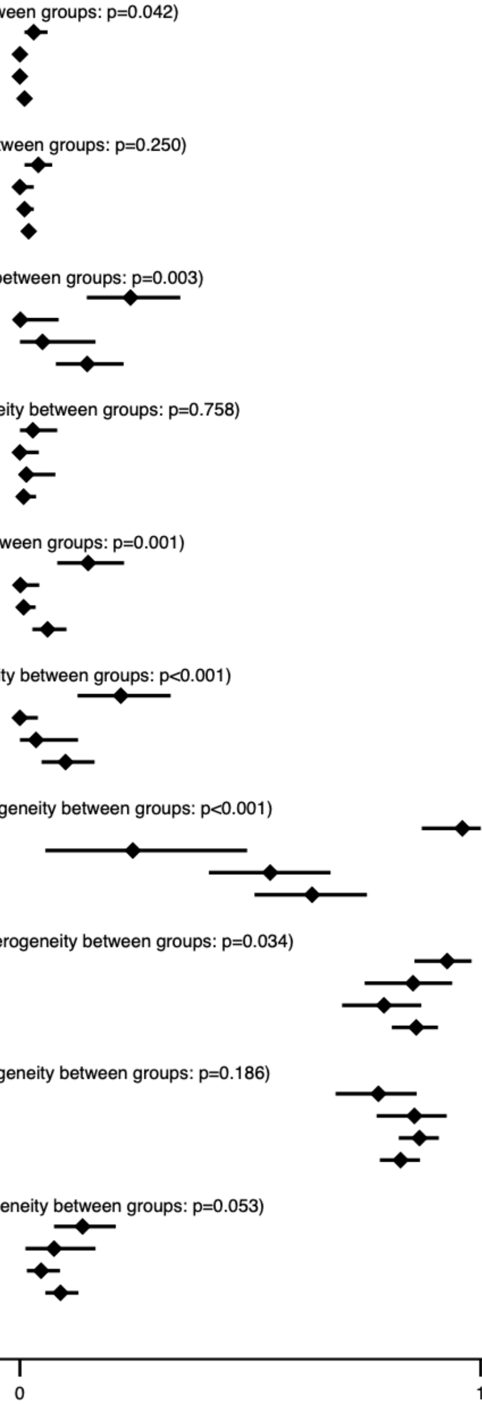
Table 3 Additional morbidity outcomes sub-divided by treatment group

	Number of events / patients			
Outcome	**Overall (%)**	**Open (%)**	**FDS (%)**	**Endo (%)**
Perioperative Ischemic Stroke	89/983 (9.1)	44/290 (15.2)	5/116 (4.3)	40/577 (6.9)
Perioperative Hydrocephalus	103/370 (27.8)	66/172 (38.4)	19/97 (19.6)	18/101 (17.8)
Perioperative Vasospasm	163/694 (23.5)	80/325 (24.6)	4/48 (8.3)	79/321 (24.6)
Stenosis of Parent Artery	63/541 (11.6)	43/290 (14.8)	7/69 (10.1)	13/182 (7.1)
Postoperative Vasospasm	89/447 (19.9)	78/303 (25.7)	1/33 (3.0)	10/111 (9.0)
Postoperative Infarction	119/750 (15.9)	101/379 (26.6)	2/79 (2.5)	16/292 (5.5)
Postoperative Hydrocephalus	65/412 (15.8)	56/239 (23.4)	1/72 (1.38)	8/101 (7.9)
FU mRS (0-2)	729/840 (86.8)	281/350 (80.3)	100/111 (90.1)	348/379 (91.8)
FU mRS (3-5)	111/840 (13.2)	69/350 (19.7)	11/111 (9.9)	31/379 (8.2)



*Note: p-values are for comparisons to FDS unless specified for Overall

Group	Number of Studies	ES (95% CI)	p-value
Postoperative Mortality (Heterogeneity between groups: p=0.042)			
Open	50	0.03 (0.01, 0.06)	0.061
FDS	18	0.00 (0.00, 0.01)	
non-FDS Endovascular	42	0.00 (0.00, 0.01)	0.701
Overall		0.01 (0.00, 0.02)	0.042
Postoperative Rebleeds (Heterogeneity between groups: p=0.250)			
Open	40	0.04 (0.01, 0.07)	
FDS	16	0.00 (0.00, 0.03)	
non-FDS Endovascular	33	0.01 (0.00, 0.03)	
Overall		0.02 (0.01, 0.03)	0.25
Postoperative Vasospasm (Heterogeneity between groups: p=0.003)			
Open	22	0.24 (0.14, 0.35)	0.002
FDS	7	0.00 (0.00, 0.08)	
non-FDS Endovascular	10	0.05 (0.00, 0.16)	0.519
Overall		0.15 (0.08, 0.22)	0.003
Postoperative Distal Embolism (Heterogeneity between groups: p=0.758)			
Open	6	0.03 (0.00, 0.08)	
FDS	7	0.00 (0.00, 0.04)	
non-FDS Endovascular	6	0.01 (0.00, 0.08)	
Overall		0.01 (0.00, 0.04)	0.758
Postoperative Infarction (Heterogeneity between groups: p=0.001)			
Open	30	0.15 (0.08, 0.23)	0.002
FDS	13	0.00 (0.00, 0.04)	
non-FDS Endovascular	26	0.01 (0.00, 0.03)	0.682
Overall		0.06 (0.03, 0.10)	0.001
Postoperative Hydrocephalus (Heterogeneity between groups: p<0.001)			
Open	18	0.22 (0.12, 0.33)	<0.001
FDS	11	0.00 (0.00, 0.04)	
non-FDS Endovascular	11	0.04 (0.00, 0.13)	0.164
Overall		0.10 (0.05, 0.16)	<0.001
Postoperative Complete Occlusion (Heterogeneity between groups: p<0.001)			
Open	10	0.96 (0.87, 1.00)	<0.001
FDS	4	0.25 (0.05, 0.49)	
non-FDS Endovascular	25	0.54 (0.41, 0.67)	0.037
Overall		0.63 (0.51, 0.75)	<0.001
Complete Occlusion at last Follow-up (Heterogeneity between groups: p=0.034)			
Open	27	0.93 (0.86, 0.98)	0.138
FDS	18	0.85 (0.75, 0.94)	
non-FDS Endovascular	31	0.79 (0.70, 0.87)	0.385
Overall		0.86 (0.81, 0.91)	0.034
Good (0-2) mRS at Last Follow-up (Heterogeneity between groups: p=0.186)			
Open	30	0.78 (0.69, 0.86)	
FDS	17	0.86 (0.77, 0.93)	
non-FDS Endovascular	29	0.87 (0.82, 0.91)	
Overall		0.83 (0.78, 0.87)	0.186
Poor (3-5) mRS at Last Follow-up (Heterogeneity between groups: p=0.053)			
Open	33	0.14 (0.07, 0.21)	
FDS	17	0.07 (0.01, 0.16)	
non-FDS Endovascular	27	0.05 (0.01, 0.09)	
Overall		0.09 (0.05, 0.13)	0.053



*Note: p-values are for comparisons to FDS unless specified for Overall

Contributorship Statement:

J.N.J and A.S.H conceived and organized project. W.W. and J.N.J conceived the statistical design. A.O., A.S.H, V.E.S and S.E.R led to the literature search and data extraction and T.Y.E.A and J.N.J supervised this process with interval quality review and adjudication of any questions or disputes. W.W. performed the analysis and ASH, V.E.S and the entire authorship group reviewed and approved the statistical analysis and its interpretation via virtual meeting sessions. S.E.R, N.S.S, and V.E.S spearheaded and W.W., A.S.H and J.N.J contributed to the manuscript initial draft composition and all authors contributed to the revision process with J.N.J supervision and final approval of the final draft.

Abbreviations used in this paper*: BBA = blood blister aneurysm, ACA = anterior cerebral artery; ACoA = anterior communicating artery; SAH = subarachnoid hemorrhage; ICA = internal carotid artery; ICP = intracranial pressure; MCA = middle cerebral artery; PCoA = posterior communicating artery, mRS = modified Rankin scale; FDS = flow-diverting stents*

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: