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Flow-diverting device versus coil embolization for unruptured intracranial aneurysm

A meta-analysis

Jia-Lin Xia, MD[a,*], Guang-Lei Li, MD[a], Hong-En Liu, MD[a], Xia Feng-Fei, MD[b], Xin-Dong Gu, MD[b]

Abstract

Background: Both coil embolization (CE) and flow-diverting device (FDD) placement are widely used for treatment of intracranial aneurysms (IAs). The aim of this meta-analysis is to compare the relative clinical safety and efficacy of FDD and CE for the treatment of unruptured IAs.

Methods: The PubMed, Embase, and Cochrane Library databases were searched for relevant studies from the date of inception through April 2020. The primary endpoint for this meta-analysis was the 6-month rate of complete occlusion, while secondary endpoints included rates of retreatment, complications, and parental arterial patency.

Results: This meta-analysis includes 8 studies, which included 839 total patients that underwent FDD and 2734 that underwent CE. FDD group exhibited a significantly higher pooled 6-month complete occlusion rate ($P = .02$). The subgroup analysis demonstrated that FDD treatment was associated with significantly higher pooled 6-month complete occlusion rates in patients with large or giant IAs ($P < .00001$), whereas no differences in 6-month complete occlusion rates were observed between the FDD and CE groups of patients with non-large/giant IAs ($P = .83$). The pooled retreatment ($P = .16$) and complication ($P = .15$) rates were comparable between 2 groups. The CE group exhibited significantly higher pooled parent artery patency rate ($P = .01$). The funnel plots did not reveal any evidence of publication bias.

Conclusions: FDDs can be used to effectively and safely treat large and giant IAs, achieving higher rates of complete occlusion than CE treatment. For non-large/giant IAs, we observed comparable efficacy between FDD and CE treatments.

Abbreviations: CE = coil embolization, CI = confidence intervals, FDD = flow-diverting device, HR = hazard ratios, IA = intracranial aneurysm, OR = odds ratio.

Keywords: coil, flow-diverting device, intracranial aneurysm, meta-analysis

1. Introduction

Intracranial aneurysms (IAs) are disorders that result in vascular abnormalities within the brain, affecting upwards of 2% to 3% of the general population.[1–4] IA rupture can lead to potentially lethal subarachnoid hemorrhage, with IAs > 10 mm in diameter being at an elevated risk of rupture.[5]

IAs are now routinely treated via well-established endovascular treatment strategies,[6,7] with coil embolization (CE) strategies including normal CE, balloon-assisted CE, and stent-assisted CE having been utilized in this therapeutic context for roughly 3 decades.[8–10] Despite their widespread use, CE approaches exhibit relatively low rates of complete occlusion, and are additionally associated with high rates of recurrence, particularly when used to treat large and giant IAs.[11] While stent-assisted CE can help achieve more durable treatment outcomes, high recurrence rates (20–57%) nonetheless persist in treated patients.[12–14]

The flow-diverting device (FDD) approach is a novel strategy that has revolutionized IA treatment, shifting the interventional approach from an endovascular approach to an endoluminal strategy.[15] FDDs facilitate parental artery endoluminal reconstruction while directing blood flow away from the IA sac, thereby facilitating endoluminal reconstruction.[16] A meta-analysis conducted in 2016 compared the relative efficacy of CE and FDDs for IA treatment and determined that FDD treatment was associated with a satisfactory rate of complete occlusion.[1] However, some of the studies included in that prior meta-analysis exhibited an imbalance in IA patient status (ruptured vs unruptured), potentially impacting observed results.[1] There have additionally been multiple studies published comparing CE and FDD approaches for the treatment of IAs since the publication of this previous meta-analysis.[17–19]

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Neuro-surgery, [b] Department of Interventional Treatment, Binzhou People's Hospital, Binzhou, China.

[*] Correspondence: Jia-Lin Xia, Department of Neuro-surgery, Binzhou People's Hospital, No. 7 Huanghe Road, Binzhou, China (e-mail: 13589425766@163.com).

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As such, we herein conducted a new meta-analysis aimed at comparing the relative clinical safety and efficacy of FDD and CE for the treatment of unruptured IAs.

2. Materials and methods

2.1. Study selection

This meta-analysis was approved by the Institutional Review Board of Binzhou People's Hospital. The PubMed, Embase, and Cochrane Library databases were searched for relevant studies from the date of inception through April 2020 using the following search terms: flow diverting, flow diverter, covered stent, stent-graft, coil, intracranial aneurysm, and cerebral aneurysm.

Study inclusion criteria included: studies were either non-randomized comparative analyses or were randomized controlled trials (RCTs) that compared FDD and CE for the treatment of unruptured IAs; and studies were published in English.

Studies were excluded if they were: non-comparative studies; animal or other preclinical studies; and review articles.

2.2. Data extraction

Two investigators independently extracted data from all identified articles, with the corresponding author helping to resolve any inconsistencies in the extracted data. Extracted items included: study baseline data, patient baseline data, and treatment-associated data.

2.3. Quality assessment

The 8-point revised Jadad composite scale was used to gauge the quality of all included RCTs.[20] High-quality RCTs were those with scores ≥4 points.[20] The 9-point Newcastle–Ottawa scale was used to evaluate all non-RCTs, with studies being deemed of high quality if they were associated with scores ≥5.[21]

2.4. Endpoints

The primary endpoint for this meta-analysis was the 6-month rate of complete occlusion, while secondary endpoints included rates of re-treatment, complications, and parental arterial patency. Complete occlusion and arterial patency were confirmed via 3D rotational angiography.

2.5. Statistical analyses

RevMan v5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration) and Stata v12.0 (StataCorp, College Station, TX, USA) were used for all data analyses. The Mantel–Haenszel method was used to measure pooled odds ratios (ORs) and 95% confidence intervals (CIs) for dichotomous variables, whereas continuous variables were analyzed based upon mean difference (MD) and 95% CIs. Study heterogeneity was assessed via X^2 and I^2 tests, with $I^2 > 50\%$ being indicative of significant heterogeneity. Fixed-effects models were used for analyses when significant heterogeneity was not detected, whereas random-effects models were used in the presence of significant heterogeneity. Causes of heterogeneity were evaluated via sensitivity and subgroup analyses. Sensitivity analysis was carried out to investigate the cause of inter-trial heterogeneity by removing each included study sequentially. Subgroup analysis was performed based on the size of IAs. Funnel plots and Egger bias test were used to assess the risk of bias. The Egger bias test was performed using Stata v12.0. $P < .05$ was considered as a significant publication bias.

3. Results

3.1. Study characteristics

Our initial search strategy identified 103 potentially relevant studies, of which 8 were ultimately included in our final meta-analysis (Fig. 1). These included 7 retrospective studies[16,17,19,22–25] and 1 RCT,[18] all of which were considered to be of high quality (Table 1).

These 8 studies included 839 total patients that had undergone FDD treatment and 2734 that had undergone CE treatment (Table 2). Three studies were specifically focused on patients exhibiting large or giant (≥10 mm) IAs.[16–18]

3.2. Treatment-associated rates of 6-month complete occlusion

We were able to extract data pertaining to the rate of 6-month complete occlusion from 5 studies.[16–18,22,24] We found that the FDD treatment group exhibited a significantly higher pooled 6-month complete occlusion rate (OR: 0.28; 95% CI: 0.09–0.85; $P = .02$, Fig. 2A). Significant heterogeneity was detected among the included studies ($I^2 = 82\%$; $P = .0002$), whereas no significant risk of publication bias was detected (Egger test, $P = .477$).

A sensitivity analysis did not exhibit any significant changes in overall heterogeneity following the omission of any individual study from our overall analysis. We additionally conducted subgroup analyses based upon the size of IAs in treated patients (Fig. 2B). FDD treatment was associated with significantly higher pooled 6-month complete occlusion rates in patients with large or giant IAs (OR: 0.12; 95% CI: 0.07–0.21; $P < .00001$), whereas no differences in 6-month complete occlusion rates were observed between the FDD and CE groups of patients with non-large/giant IAs (OR: 1.10; 95% CI: 0.46–2.60; $P = .83$). In addition, we did not detect significant heterogeneity within either of these subgroups ($I^2 = 0\%$ and 18%, respectively). However, the significant subgroup heterogeneity was found in the test of subgroup differences. Therefore, the significant heterogeneity of 6-month complete occlusion rates might be caused by the different IA size.

3.3. Retreatment

We were able to extract data pertaining to retreatment rates from 5 of the included studies.[16,19,22,24,25] We observed comparable pooled retreatment rates between the 2 groups (OR: 0.46; 95% CI: 0.15–1.38; $P = .16$, Fig. 3). We also observed significant heterogeneity among the included studies ($I^2 = 72\%$; $P = .0007$), although no evidence of publication bias was detected through funnel plot and Egger test analyses (Egger test, $P = .080$).

When the study conducted by Chalouhi et al[16] in 2013 was omitted, this significant heterogeneity was no longer evident ($I^2 = 43\%$; $P = .15$). Even when this study was omitted, however, we did not observe any significant differences in retreatment rates between these 2 patient groups (OR: 0.77; 95% CI: 0.35–1.69; $P = .52$).

3.4. Complications

We were able to extract data pertaining to complication rates from 7 included studies.[16–18,22–25] Pooled complication rates were

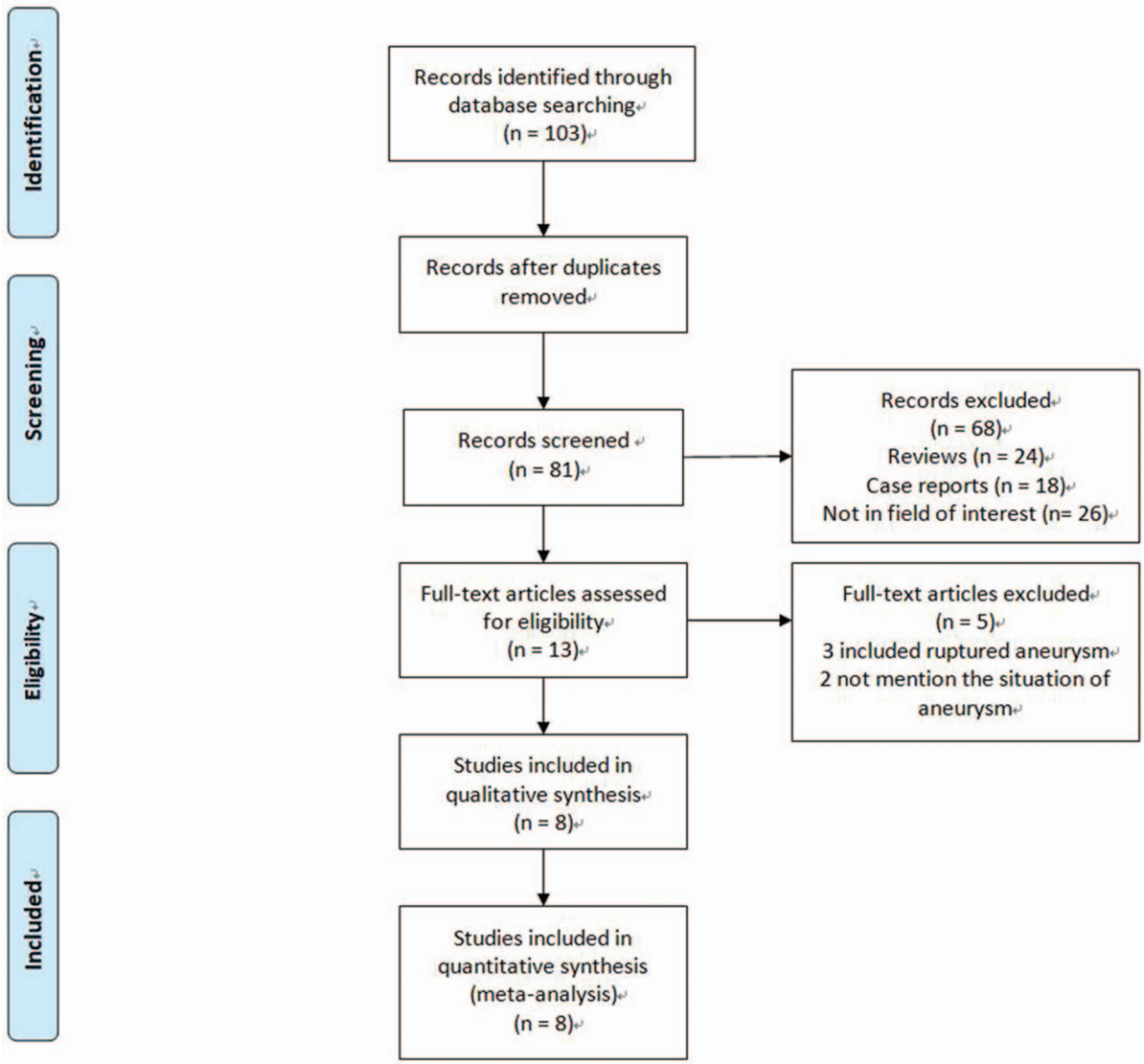

Figure 1. The flowchart of this study.

similar before these 2 treatment groups (OR: 1.44; 95% CI: 0.88–2.37; $P = .15$, Fig. 4), with no evidence of significant heterogeneity ($I^2 = 0\%$; $P = .49$). There was also no evidence of publication bias in funnel plot and Egger test analyses (Egger test, $P = .263$).

3.5. Parent artery patency

We were able to extract data pertaining to parental artery patency for 3 of the included studies.[17,18,25] We found that patients in the CE group exhibited significantly higher pooled parent artery patency rate (OR: 4.96; 95% CI: 1.48–16.69; $P = .01$, Fig. 5). There was no significant heterogeneity among these studies ($I^2 = 46\%$; $P = .16$). The funnel plot and Egger test did not reveal any evidence of publication bias (Egger test, $P = .507$).

4. Discussion

In the present meta-analysis, we assessed differences in the clinical safety and efficacy of FDD and CE for the treatment of unruptured IAs. We found that FDD treatment was associated with significantly higher 6-month complete occlusion rates. However, the significant heterogeneity made this result is not very reliable. The sources of heterogeneity might be from many aspects, which include size of IAs, methodology used, follow-up time, and geographical locations. The size of IAs and methodology used may be the important factors which caused the heterogeneity of 6-month complete occlusion rates. For technique of the CE, 4 included studies used stent-assist CE,[16,17,22,24] while only 1 study did not show the details of technique of the CE.[18] Therefore, the technique of the CE may not be the factor of heterogeneity. Furthermore, we made the subgroup analysis based on the size of IAs and the subgroup analysis suggested that significantly higher pooled 6-month complete occlusion rate was only found in patients with large or giant IAs. Indeed, IA size was a major source of heterogeneity in the 6-month complete occlusion rate data set.

While there have been a number of technical improvements to the procedure, there are still limitations to the use of CE for the

Table 1

Baseline data of the 8 studies.

Study	Year	Design	Country	Focused on giant aneurysm	Quality assessments	
					Revised Jade score	Newcastle–Ottawa score
Chalouhi[16]	2013	Retrospective	America	Yes	–	8
Chalouhi[22]	2014	Retrospective	America	No	–	7
Kim[23]	2014	Retrospective	Korea	No	–	8
Di Maria[24]	2015	Retrospective	France	No	–	8
Durst[25]	2016	Retrospective	America	No	–	7
Zhang [17]	2016	Retrospective	China	Yes	–	6
Liu[18]	2018	RCT	China	Yes	5	–
Fukuda[19]	2019	Retrospective	Japan	No	–	6

RCT = randomized controlled trial.

treatment of IAs. For one, CE approaches are not well-suited to use for the treatment of fusiform or very large IAs.[1] In addition, even in cases where complex IAs can be feasibly treated via CE, long-term occlusion cannot be guaranteed. Furthermore, the use of a large number of coils in IAs can perpetuate a mass effect and thereby result in thromboembolic complications and high treatment costs.[1] Lastly, CE approaches are not able to avoid direct contact with aneurysms, thereby significantly increasing the potential for intraprocedural rupture.

FDDs are generally designed in an effort to provide a mesh with small cells that exhibits high coverage and longitudinal flexibility, with the goal of redirecting blood flow along the longitudinal axis of the target vessel and thereby decreasing outflow and inflow of the IA, thereby leading to eventual thrombosis and obliteration of the aneurysm. FDDs also allows for the maintenance of appropriate blood flow in jailed branches and perforators.[1]

We detected comparable pooled retreatment rates when comparing the FDD and CE groups in the present meta-analysis. This is in contrast to the results of Chalouhi et al,[16] who observed higher retreatment rate in the CE group (37% vs 2.8%, $P < .001$). This study thus represented a source of significant heterogeneity in our meta-analysis, as it focused specifically on patients with large or giant IAs. When we removed the Chalouhi et al[16] study, we still did not observe any significant differences in retreatment rates between these 2 patient groups ($P = .52$). Therefore, we can believe that FDD and CE provide similar clinical effectiveness for non-large/giant IAs. Furthermore, these findings may suggest that FDDs are capable of improving angiographic outcomes in those patients exhibiting large unruptured IAs. However, for the endpoint of retreatment, only 1 study focused on the large IAs. Additional studies are still required.

In studies not focused on large or giant IAs,[19,22,24,25] we observed comparable rates of pooled 6-month complete occlusion ($P = .83$) and retreatment ($P = .52$) when comparing the CE and FDD groups. This may suggest that FDDs do not offer any significant advantages of CE when used to treat non-large/giant IAs.

Our results suggest that FDD and CE treatment approaches offer similar safety profiles when used to treat IAs. In one prior meta-analysis of 29 studies,[26] FDDs were associated with respective procedure-related morbidity and mortality rates of 5% and 4%, while limited CE case series results indicated that this treatment approach was associated with an 11% overall complication rate.[13] In this study, however, we found that pooled parent artery patency rates were significantly higher among patients in the CE group. The primary cause of occlusion of the parent artery is in-stent thrombosis.[17] One systematic

Table 2

Characteristics of the included studies.

Study	Groups	Patients	Mean age, y	Mean lesion size, mm	Mean follow-up	Coil techniques
Chalouhi[16]	FDD	40	60.7	14.9	8 months	Stent/balloon-assist coil; Normal coil
	Coil	120	60.3	14.9	15 months	
Chalouhi[22]	FDD	40	52.1	6.2	Not given	Stent-assist coil
	Coil	160	52.6	6.0	Not given	
Di Maria[24]	FDD	77	49.2	6.7	>12 months	Stent-assist coil; normal coil
	Coil	61	49.7	8.7	>12 months	
Kim[23]	FDD	24	53.2	10.2	6 month	Stent-assist coil
	Coil	38	55.9	8.9	23 month	
Durst[25]	FDD	19	53.2	10.5	Not given	Not mentioned in details
	Coil	38	57.4	9.6	Not given	
Zhang[17]	FDD	45	Not given	All >10	Not given	Stent-assist coil
	Coil	45	Not given	All >10	Not given	
Liu[18]	FDD	82	52.1	All >10	Not given	Not mentioned in details
	Coil	62	55.7	All >10	Not given	
Fukuda[19]	FDD	512	62.8	Not given	Not given	Stent-assist coil; normal coil
	Coil	2210	63.6	Not given	Not given	

FDD = flow-diverting device.

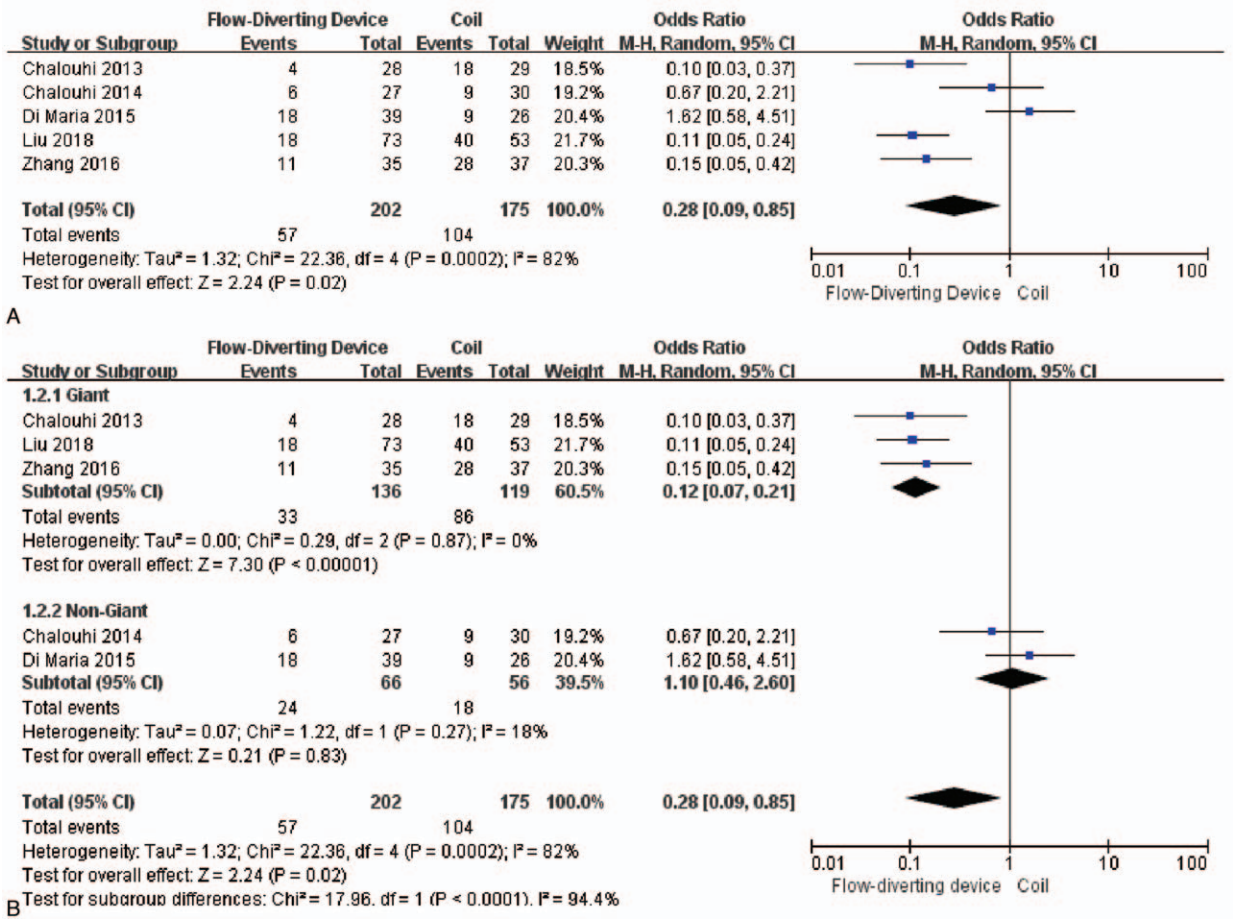

Figure 2. (A) The pooled 6-month complete occlusion rate was significant higher in the FDD group. (B) The subgroup analysis demonstrated that the pooled 6-month complete occlusion rate was significant higher in the FDD group based on the large or giant IAs. FDD = flow-diverting device, IA = intracranial aneurysm.

review of SILK stent devices found a 10.2% rate of occlusion of stented parent arteries.[27] The use of FDDs to manage IAs is dependent on the appropriate administration of preoperative medications, given that patients are at risk of competing thromboembolic complications such as delayed IA rupture and in-stent thrombosis.[28] Risk factors associated with delayed rupture following FDD placement must be assessed in order to definitively establish the indications of this technique, which perioperative medications are most therapeutically appropriate, and what methodological approaches are employed (with or without additional coils).

There are certain limitations to the present meta-analysis. For one, the majority of the included studies were retrospective in nature, potentially resulting in selective bias. As additional high-quality RCTs become available, we will conduct a specific and more focused analysis of these results. Second, we observed significant heterogeneity for many of the outcomes in the present study. While we conducted sensitivity and subgroup analyses in

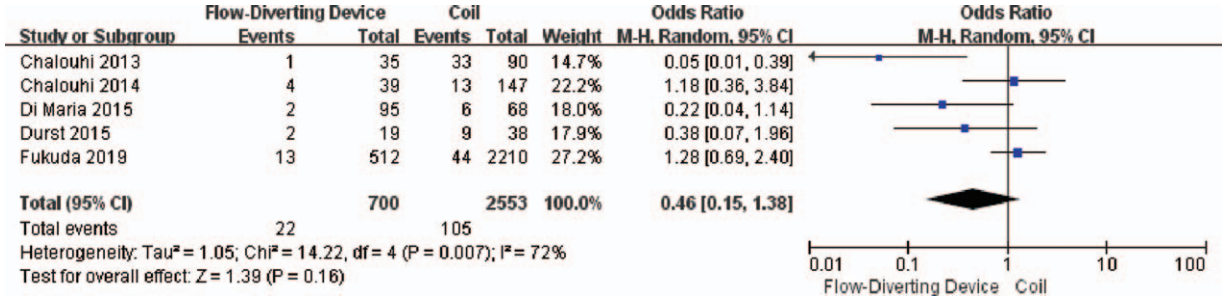

Figure 3. The pooled retreatment rates were comparable between the 2 groups.

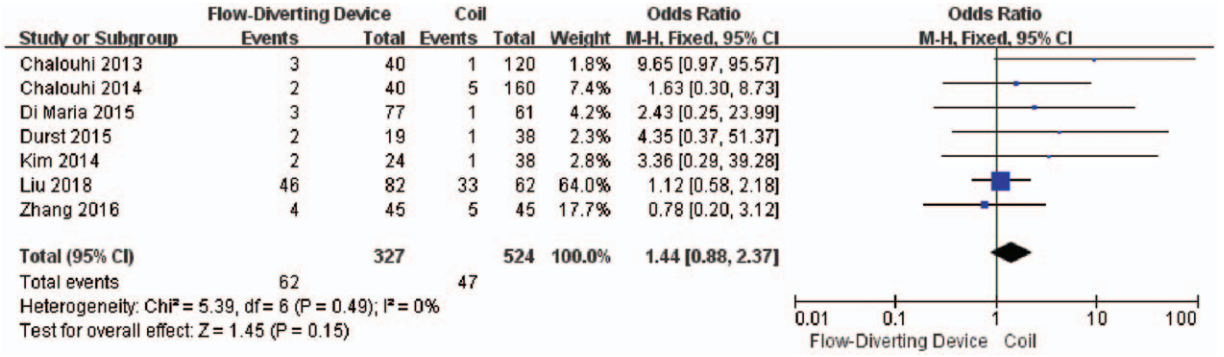

Figure 4. The pooled complication rates were comparable between the 2 groups.

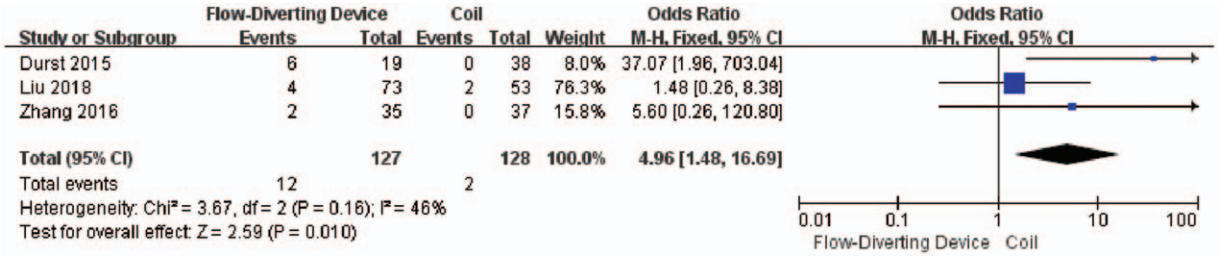

Figure 5. Significantly higher pooled parent artery patency rate was found in the CE group. CE = coil embolization.

an effort to identify the causes of such heterogeneity, further high-quality studies are essential. Third, many of the included studies employed a range of CE approaches (normal, stent-assisted, or balloon-assisted CE), thus potentially limiting the applicability of our conclusions.

In summary, FDDs can be used to effectively and safely treat large and giant IAs, achieving higher rates of complete occlusion than CE treatment. For non-large/giant IAs, we observed comparable efficacy between FDD and CE treatments, with the latter potentially being associated with better long-term parent artery patency.

Author contributions

Conceptualization: Jia-Lin Xia.
Data curation: Hong-En Liu, Xia Feng-Fei, Xin-Dong Gu.
Formal analysis: Guang-Lei Li, Hong-En Liu.
Methodology: Guang-Lei Li.
Writing – original draft: Jia-Lin Xia.
Writing – review & editing: Jia-Lin Xia.

References

[1] Zhou G, Zhu YQ, Su M, et al. Flow-diverting devices versus coil embolization for intracranial aneurysms: a systematic literature review and meta-analysis. World Neurosurg 2016;88:640–5.
[2] Brown RDJr, Broderick JP. Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening. Lancet Neurol 2014;13:393–404.
[3] Li MH, Chen SW, Li YD, et al. Prevalence of unruptured cerebral aneurysms in Chinese adults aged 35 to 75 years: a cross-sectional study. Ann Intern Med 2013;159:514–21.
[4] Molyneux AJ, Kerr RS, Birks J, et al. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardized mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. Lancet Neurol 2009;8:427–33.
[5] Morita A, Kirino T, Hashi K, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. N Engl J Med 2012;366:2474–82.
[6] McDonald JS, McDonald RJ, Fan J, Kallmes DF, Lanzino G, Cloft HJ. Comparative effectiveness of unruptured cerebral aneurysm therapies: propensity score analysis of clipping versus coiling. Stroke 2013;44:988–94.
[7] Lin N, Cahill KS, Frerichs KU, Friedlander RM, Claus EB. Treatment of ruptured and unruptured cerebral aneurysms in the USA: a paradigm shift. J Neurointerv Surg 2012;4:182–9.
[8] Guglielmi G, Viñuela F, Dion J, Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: preliminary clinical experience. J Neurosurg 1991;75:8–14.
[9] Higashida RT, Smith W, Gress D, et al. Intravascular stent and endovascular coil placement for a ruptured fusiform aneurysmof the basilar artery. Case report andreview of the literature. J Neurosurg 1997;87:944–9.
[10] Moret J, Cognard C, Weill A, et al. Reconstruction technic in the treatment of wideneck intracranial aneurysms. Long-term angiographic and clinical results. Apropos of 56 cases. J Neuroradiol 1997;24:30–44.
[11] Raymond J, Guilbert F, Weill A, et al. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. Stroke 2003;34:1398–403.
[12] Chalouhi N, Tjoumakaris S, Gonzalez LF, et al. Coiling of large and giant aneurysms: complications and long-term results of 334 cases. AJNR Am J Neuroradiol 2014;35:546–52.
[13] Wang B, Gao BL, Xu GP, et al. Endovascular embolization is applicable for large and giant intracranial aneurysms: experience in one center with long-term angiographic follow-up. Acta Radiol 2015;56:105–13.
[14] Consoli A, Vignoli C, Renieri L, et al. Assisted coiling of saccular wide-necked unruptured intracranial aneurysms: stent versus balloon. J Neurointerv Surg 2016;8:52–7.

[15] Zhou Y, Yang PF, Fang YB, et al. A novel flow-diverting device (Tubridge) for the treatment of 28 large or giant intracranial aneurysms: a single-center experience. AJNR Am J Neuroradiol 2014;35:2326–33.
[16] Chalouhi N, Tjoumakaris S, Starke RM, et al. Comparison of flow diversion and coiling in large unruptured intracranial saccular aneurysms. Stroke 2013;44:2150–4.
[17] Zhang Y, Zhou Y, Yang P, et al. Comparison of the flow diverter and stent-assisted coiling in large and giant aneurysms: safety and efficacy based on a propensity score-matched analysis. Eur Radiol 2016;26:2369–77.
[18] Liu JM, Zhou Y, Li Y, et al. Parent artery reconstruction for large or giant cerebral aneurysms using the tubridge flow diverter: a multicenter, randomized, controlled clinical trial (PARAT). AJNR Am J Neuroradiol 2018;39:807–16.
[19] Fukuda H, Sato D, Kato Y, et al. Comparing retreatments and expenditures in flow diversion versus coiling for unruptured intracranial aneurysm treatment: a retrospective cohort study using a Real-World National Database. Neurosurgery 2020;87:63–70.
[20] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
[21] Wells GA, Shea BJ, O'Connell D, et al. The Newcastle–Ottawa scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Appl Eng Agric 2000;18:727–34.
[22] Chalouhi N, Starke RM, Yang S, et al. Extending the indications of flow diversion to small, unruptured, saccular aneurysms of the anterior circulation. Stroke 2014;45:54–8.
[23] Kim LJ, Tariq F, Levitt M, et al. Multimodality treatment of complex unruptured cavernous and paraclinoid aneurysms. Neurosurgery 2014;74:51–61.
[24] Di Maria F, Pistocchi S, Clarençon F, et al. Flow diversion versus standard endovascular techniques for the treatment of unruptured carotid-ophthalmic aneurysms. AJNR Am J Neuroradiol 2015;36: 2325–30.
[25] Durst CR, Starke RM, Clopton D, et al. Endovascular treatment of ophthalmic artery aneurysms: ophthalmic artery patency following flow diversion versus coil embolization. J Neurointerv Surg 2016;8: 919–22.
[26] Brinjikji W, Murad MH, Lanzino G, et al. Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. Stroke 2013;44:442–7.
[27] Murthy SB, Shah S, Shastri A, et al. The SILK flow diverter in the treatment of intracranial aneurysms. J Clin Neurosci 2014;21:203–6.
[28] Kulcsár Z, Houdart E, Bonafé A, et al. Intra-aneurysmal thrombosis as a possible cause of delayed aneurysm rupture after flow-diversion treatment. Am J Neuroradiol 2011;32:20–5.