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ABSTRACT

BACKGROUND AND PURPOSE: Flow diversion is a recent endovascular treatment for intracranial aneurysms. We compared the safety and efficacy of flow diversion with the alternative standard management options.

MATERIALS AND METHODS: A parallel group, prerandomized, controlled, open-label pragmatic trial was conducted in 3 Canadian centers. The trial included all patients considered for flow diversion. A Web-based platform 1:1 randomly allocated patients to flow diversion or 1 of 4 alternative standard management options (coiling with/without stent placement, parent vessel occlusion, surgical clipping, or observation) as prespecified by clinical judgment. Patients ineligible for alternative standard management options were treated with flow diversion in a registry. The primary safety outcome was death or dependency (mRS > 2) at 3 months. The composite primary efficacy outcome included the core lab–determined angiographic presence of a residual aneurysm, aneurysm rupture, progressive mass effect during follow-up, or death or dependency (mRS > 2) at 3–12 months.

RESULTS: Between May 2011 and November 2020, three hundred twenty-three patients were recruited: Two hundred seventy-eight patients (86%) had treatment randomly allocated (139 to flow diversion and 139 to alternative standard management options), and 45 (14%) received flow diversion in the registry. Patients in the randomized trial frequently had unruptured (83%), large (52% ≥10 mm) carotid (64%) aneurysms. Death or dependency at 3 months occurred in 16/138 patients who underwent flow diversion and 12/137 patients receiving alternative standard management options (relative risk, 1.33; 95% CI, 0.65–2.69; P = .439). A poor primary efficacy outcome was found in 30.9% (43/139) with flow diversion and 45.6% (62/136) of patients receiving alternative standard management options, with an absolute risk difference of 14.7% (95% CI, 3.3%–26.0%; relative risk, 0.68; 95% CI, 0.50–0.92; P = .014).

CONCLUSIONS: For patients with mostly unruptured, large, anterior circulation (carotid) aneurysms, flow diversion was more effective than the alternative standard management option in terms of angiographic outcome.

ABBREVIATIONS: ASMO = alternative standard management option; DSMC = Data Safety and Monitoring Committee; FD = flow diversion; FIAT = Flow Diversion in Intracranial Aneurysm Treatment; PVO = parent vessel occlusion; RCT = randomized controlled trial

Flow diversion (FD) is an innovative treatment of intracranial aneurysms.[1-3] Flow diverters are low-porosity, braided endovascular stent devices designed to normalize flow in a vessel with an aneurysm and occlude the aneurysm by thrombosis of the sac.[4] FD can often accomplish what other interventions cannot, such as reconstructing a cerebral vessel having a giant aneurysm and occluding the aneurysm while preserving normal parent and branching vessels.[5] Yet FD has also been associated with unexpected delayed complications, such as aneurysm ruptures, parenchymal hematomas at a distance from the aneurysm, and strokes from stent thrombosis.[6,7] First approved in 2011 in the United States for the treatment of unruptured, large and giant aneurysms of the proximal segments of the carotid artery,[2] clinical usage has since expanded to aneurysms of all sizes, locations, and presentations. More than 22 systematic reviews of case series have shown aneurysm occlusion rates exceeding 75%, with treatment-related morbidity and mortality

in the range of 2%–10%.[1,3,8,9] The role that FD should play in clinical practice still remains unclear because opinions and practices vary widely[10] and randomized comparisons with standard management options are few. Two randomized trials were published in 2018; both restricted inclusion to large or complex anterior circulation aneurysms treatable by only 1 specific comparator intervention. One comparison of FD with stent-assisted coiling in 144 patients raised safety concerns but showed increased rates of complete angiographic occlusions with FD.[11] Another trial in 80 patients showed FD to be safer but less effective than surgical bypass and parent vessel occlusion (PVO).[12]

The Flow Diversion in Intracranial Aneurysm Treatment (FIAT) trial was launched in 2011 to introduce to endovascular practice a promising-but-unvalidated innovation for patients with difficult intracranial aneurysms.[13,14] FIAT was pragmatic, all-inclusive, and proposed a 1:1 randomized allocation for the treatment by FD or alternative standard management options (ASMOs) (defined as any other prespecified alternative management option), along with a registry of patients treated with FD considered ineligible for ASMO.[14] The main hypothesis of the trial was that treatment with FD would increase the percentage of patients with a good outcome by 15%, a composite that included occlusion or near-occlusion of the aneurysm combined with an independent clinical outcome (mRS < 3) at 3–12 months. The aim of this article was to present the final results of the FIAT randomized trial.

MATERIALS AND METHODS

FIAT was an investigator-led, pragmatic, multicenter, randomized controlled care trial integrated into clinical practice.[13] FIAT compared a policy of using either FD (any flow diverter device with or without coiling) or ASMO to manage patients with difficult intracranial aneurysms. The ASMO was selected according to clinical judgment at the time of enrollment but before randomized allocation. Patients deemed ineligible for other management alternatives were included in a parallel FD registry. There were 3 participating Canadian centers (Montreal, Edmonton, Ottawa). All sites received institutional review board approval. The protocol was published,[14] and the trial was registered at ClinicalTrials.gov No. NCT01349582. The trial was temporarily interrupted in June 2014 for safety concerns, mainly driven by registry results, but the Data Safety and Monitoring Committee (DSMC) recommended trial continuation because treatment-related morbidity between randomized groups was similar.[15]

Patients

All patients with an aneurysm for which FD was considered a promising treatment were eligible to participate. Exclusion criteria were few: 1) severe allergy, intolerance, or bleeding disorder that precluded dual antiplatelet agents; 2) absolute contraindication to endovascular treatment or anesthesia; and 3) inability to provide consent. All patients or designees signed an informed consent form to participate in the study.

Randomization and Masking

Concealment of randomized allocation was assured through a Web-based platform. Treating physicians first had to choose, for each patient, 1 of 4 alternatives to permit computer-generated randomized allocation (1, coiling [with or without high-porosity stent placement], 2, PVO, 3, surgical clipping, and 4, conservative management). Patients ineligible for ASMO were treated with FD in a registry. The randomized allocation was stratified according to comparator intervention and center. In February 2015, the protocol was modified to allow the use of prerandomization. With prerandomization, treatment allocation (and that the planned treatment was randomly allocated) is revealed to the patient at the time of consent.[16,17] Patients who disagreed with the allocated management were still offered study participation.

Patients, interventionalists, and outcome assessors were not masked to treatment assignment, which was deemed unfeasible.

Interventions

There were no selection criteria for centers. Standard local procedures were followed. Any flow-diverting devices implanted in the parent vessel were permitted, but intra-aneurysmal flow diverters (such as the Woven EndoBridge [WEB; Microvention]) were excluded. Antiplatelet and anticoagulation regimens and testing for platelet inhibition were according to routine practice at each site. Case report forms were simple, and data were collected parsimoniously, to facilitate completion by normal care personnel.

Hypotheses, Outcomes, and Number of Patients

The safety of FD was defined in terms of the mRS scale at 3 months for all patients in the randomized controlled trial (RCT) or registry who received FD at any time: Two hundred patients could suffice to show that if the observed number of patients with mRS > 2 is 10%, the 95% CI of the percentage is from 7.0% to 14.9%.[14] The randomized trial was powered (80%) to show a 15% increase (from 75% to 90%, α error = .05; 224 patients plus losses and crossovers, for a total of 250 patients) in the percentage of patients reaching the composite primary efficacy outcome, including complete or near-complete (residual neck) angiographic occlusion of the aneurysm (3–12 months) and an independent functional outcome (mRS < 3). Clinical outcome was determined by clinicians not blinded to the treatment allocation according to a simplified, standardized mRS questionnaire.[18] The target number of patients was reached in July 2020 ($n = 250$), and a blinded report was sent to the DSMC. The DSMC recommended trial continuation to account for crossovers and patients lost to follow-up. The steering committee decided to stop inclusions on December 1, 2020, when 278 patients had been recruited to the RCT (a 24% increase over the initial estimate of 224, to account for 10% dilution of effect because of prerandomization).[19] Data entry was locked on June 1, 2021, without knowledge of outcome results.

The primary safety outcome was death or dependency (mRS > 2) at 3 months. The primary efficacy outcome was a composite of clinical and angiographic results observed at least 3–12 months after treatment. One primary poor efficacy outcome was allocated per patient; when a patient had >1 outcome, the following hierarchic order was used to classify each patient: death > mRS 3–5 (from any cause, including aneurysm rupture or progressing mass effect with the mRS assessment being made at the time of follow-up imaging) > aneurysm rupture during follow-up > retreatment during follow-up > initial treatment failure > residual aneurysm at
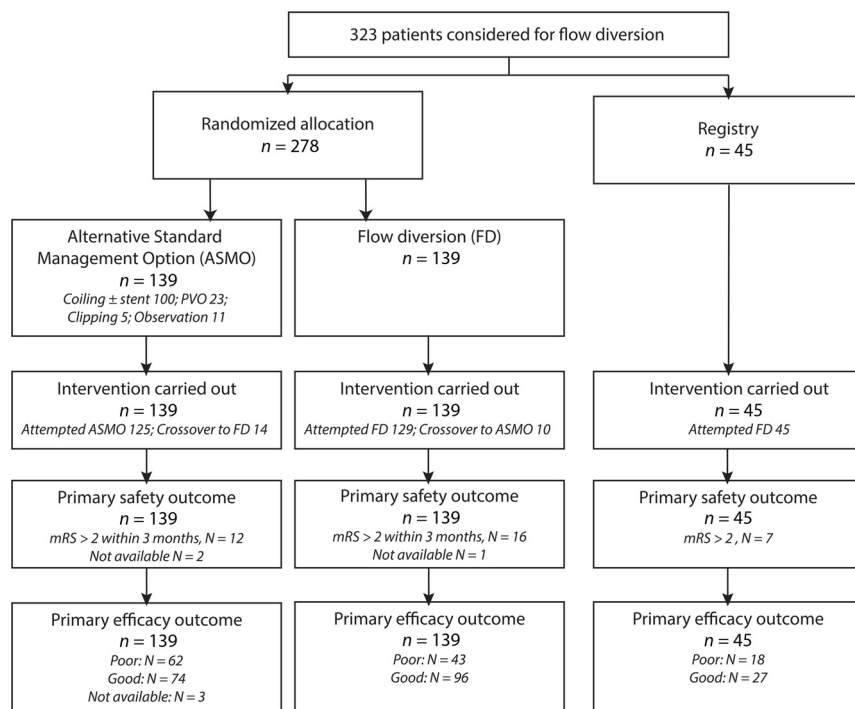
FIG 1. FIAT trial profile.

imaging follow-up (12 months) as adjudicated by an independent core lab according to a previously validated classification system.[20,21] This system includes 3 ordinal categories (complete occlusion, residual neck, residual aneurysm). The residual aneurysm category was used to adjudicate treatment failure for primary outcome analyses, and the complete occlusion category was used for exploratory analyses. The presence of various endovascular or surgical devices on imaging precluded blinding of core lab assessors.

Secondary outcomes included the individual components of the composite primary outcome as well as the mRS score at discharge and 3 and 12 months posttreatment; success in occluding the aneurysm at the end of the procedure (when appropriate); perioperative complications (ischemic strokes and intracranial hemorrhages within 1 month of the intervention); angiographic results at 12 months; length of hospital stay (number of days); discharge disposition (home, other hospital, rehabilitation facility, death); any new stroke, neurologic symptom, or sign during follow-up; and retreatment of the index aneurysm at any time.

Analyses and Statistics

Blinded data were examined at prespecified intervals by an independent DSMC, composed of an interventional neuroradiologist, a statistician, and an ethicist, but no statistical tests were performed. Three subgroups of patients were analyzed as registered: ASMO (randomly allocated), FD (randomly allocated), and registry. According to protocol, the safety analyses included all patients who were allocated to or received FD at any time. Primary analyses are intent-to-treat. The primary safety outcome was adjudicated when the mRS was >2 within 3 months of the intervention, regardless of the cause. Failure to reach the primary efficacy end point was adjudicated per patient. Primary safety and efficacy

outcomes are described using percentages and 95% confidence intervals. The impact of missing data on the conclusions was studied using sensitivity analyses in which missing data were replaced by either a good or a bad outcome. The risk difference and relative risks were estimated using a generalized estimating equation with a binomial distribution and a log- or identity-link function. The 95% confidence intervals are reported. The groups were not different with respect to risk factors for poor outcomes, and no adjustments for residual confounding factors were made.

The analyses of interactions between prespecified subgroups of interest and treatment were made by adding subgroup variables and interaction in the generalized estimating equation models. Treatment and aneurysm subgroups were examined as prespecified in 2010, regardless of the results of tests for interactions. Subgroup results according to aneurysm size (<10 mm or ≥10 mm), location (the proximal carotid artery, including the cavernous-to-superior hypophyseal segment [the initial FDA-approved FD indications], other anterior circulation, and posterior circulation aneurysms), and according to selected ASMOs before stratified randomized allocation[14] are reported. Per-protocol exploratory analyses were defined in 2 ways: "As-attempted" analyses included patients in whom FD or ASMO was attempted (regardless of randomized allocation), and "as-treated" analyses included only patients in whom FD or ASMO was actually performed at the time of the initial treatment. We also explored what results would have been if complete occlusion (rather than the combination of complete and near-complete occlusion) had been used as the criterion for a good angiographic end point, to comply with a recent FDA definition and to permit comparisons with published case series and meta-analyses. The number of adverse events within the ASMO and FD groups was compared using the χ^2 test with exact P values. Analyses were performed using SAS software, Version 9.4 (SAS Institute) and SPSS, Version 26 (IBM) with a significance level of 5%. There was no correction of P values to account for the multiplicity of exploratory analyses.

Roles of the Sponsor and Funding Source

The trial was sponsored by the Centre Hospitalier de l'Université de Montréal. The sponsor had no part in study design, conduct, or reporting, and no access to the data. There was no funding source for this study.

RESULTS

The number of patients who were registered or randomly assigned received the intended treatment and were analyzed for the safety and efficacy outcomes are shown in the trial profile (Fig 1). Of 323

Table 1: Patient and aneurysm characteristics for the randomized groups

Characteristics	Randomization	
	ASMO ($n = 139$)	FD ($n = 139$)
Age (mean) (SD)	57 (12)	58 (12)
Female (No.) (%)	108 (77.7%)	110 (79.1%)
Presentation (No.) (%)		
Asymptomatic	72 (51.8%)	78 (56.1%)
Mass effect	41 (29.5%)	40 (28.8%)
SAH	26 (18.7%)	21 (15.1%)
Aneurysm size (mm)		
Mean (SD)	13 (9)	13 (10)
Median (range)	10 (2–51)	10 (1–56)
0–9 (No.) (%)	66 (47.5%)	68 (48.9%)
10–25 (No.) (%)	59 (42.4%)	54 (38.8%)
>25 (No.) (%)	14 (10.1%)	17 (12.2%)
Aneurysm neck (mm)		
Mean (SD)	5 (3)	5 (3)
Median (min–max)	5 (2–15)	5 (1–16)
Undefined (No.) (%)	22 (15.8%)	21 (15.1%)
Location (No.) (%)		
Anterior circulation	108 (77.7%)	109 (78.4%)
Proximal carotid	71 (51.1%)	74 (53.2%)
Extradural	14 (10.1%)	21 (15.1%)
Ophthalmic	57 (41.0%)	53 (38.1%)
Other carotid	20 (14.4%)	12 (8.6%)
Other anterior	17 (12.2%)	23 (16.5%)
Posterior circulation	31 (22.3%)	30 (21.6%)

Note:—min indicates minimum; max. maximum.

Table 2: Primary efficacy outcome

	Randomization	
	ASMO ($n = 139$) (No.) (%)	FD ($n = 139$) (No.) (%)
Poor outcome	62 (44.6%)[a]	43 (30.9%)
Clinical	13 (9.4%)	12 (8.6%)
mRS >2[b]	13 (9.4%)	10 (7.2%)
Aneurysm rupture	0	2 (1.4%)
Angiographic	49 (35.3%)	31 (22.3%)
Retreatment	7 (5.0%)	5 (3.6%)
Immediate failure[c]	8 (5.8%)	7 (5.0%)
Residual aneurysm	34 (24.5%)	19 (13.7%)
Good outcome	74 (53.2%)	96 (69.1%)
Angiographic	74 (53.2%)	96 (69.1%)
Complete occlusion	60 (43.2%)	85 (61.2%)
Residual neck	14 (10.1%)	11 (7.9%)
Not available	3 (2.2%)	0

[a] It is 45.6% (62/136) when adjusting for missing data.
[b] Comprises 14 deaths (ASMO = 9/FD = 5).
[c] Immediate treatment failures are treatments that were attempted but failed, with no further angiographic follow-up.

recruited patients between May 2011 and November 2020, two hundred seventy-eight patients (86%) were randomly allocated to receive FD ($n = 139$) or ASMO ($n = 139$), and 45 (14%) received FD in the registry because they were deemed ineligible for standard options.

Patients and aneurysms compared in the randomized trial are described in Table 1. The characteristics of registry patients are described in the Online Supplemental Data. Registry patients more frequently had fusiform aneurysms with undefined necks (22/45 or 49%) than patients included in the RCT (43/278 or 16%). Randomized groups were similar. More than 80% of patients had unruptured aneurysms. Aneurysms were ≥10 mm in 52% and symptomatic in 46% of patients. The ASMO selected before randomization was coiling (with or without stent placement) in 199 patients (72%), PVO in 45 (16%), surgical clipping in 11 (4%), and observation in 23 patients (8%). The specific comparator intervention of patients actually randomized to ASMO is detailed in Fig 1.

Details of the interventions actually carried out are provided in the Online Supplemental Data. High-porosity stents were used in 36/87 patients (41%) treated by coiling ± stent placement in the ASMO group. PVO was performed using endovascular means without surgical bypass in all patients treated by PVO.

Ten patients randomly allocated to FD initially received ASMO, while 14 patients allocated to ASMO initially received FD (Fig 1 and Online Supplemental Data).

The safety of FD, predefined by protocol as mRS > 2 at 3 months in any patient treated with FD at any time ($n = 209$), is detailed in the Online Supplemental Data.

The primary safety outcome, death or dependency at 3 months from any cause, occurred in 16 of 138 (11.5%; 95% CI, 6.9%–
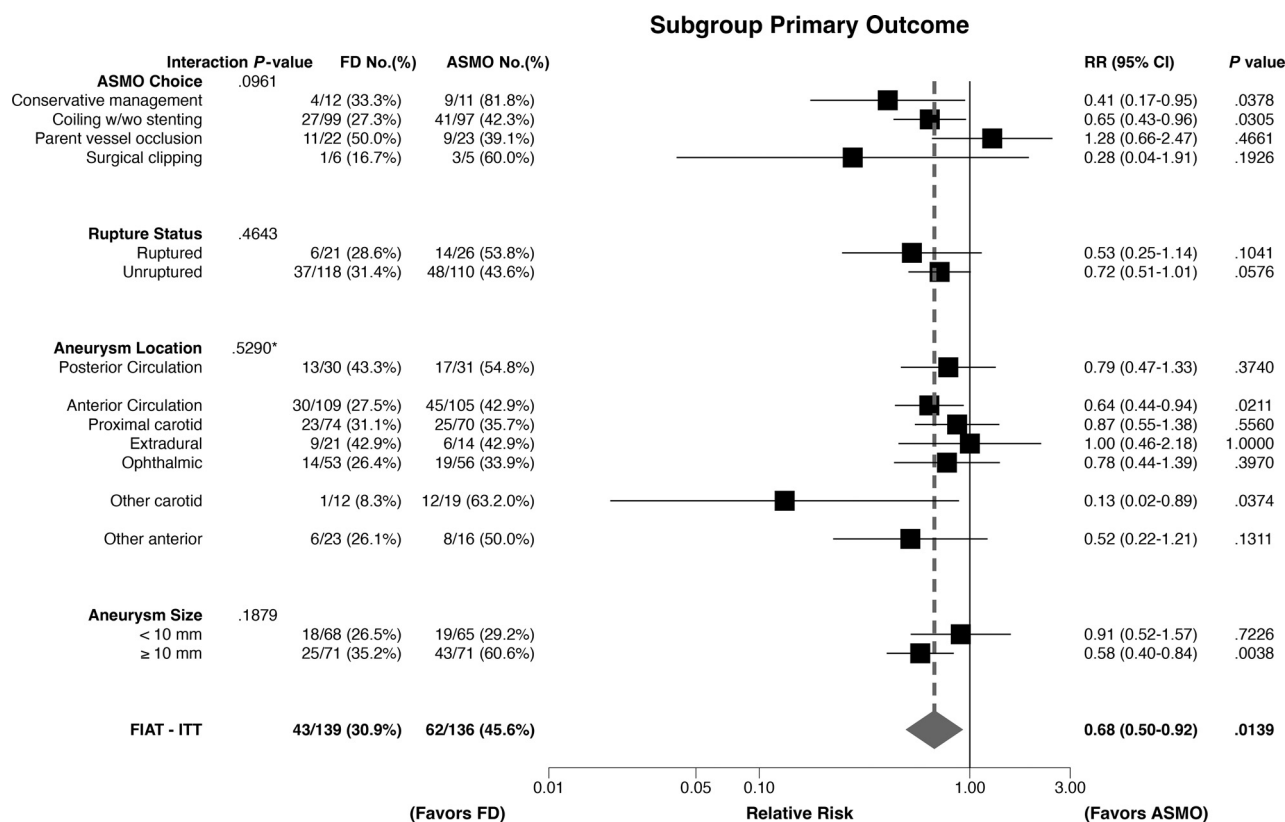
18.3%) patients randomly allocated to FD and in 12 of 137 (8.6%; 95% CI, 4.7%–14.9%) patients allocated to ASMO (relative risk, 1.33; 95% CI, 0.65–2.69; $P = 0.439$) (Fig 1; details in the Online Supplemental Data). The most frequent causes of death or dependency at 3 months were thromboembolic ($n = 14$; ASMO = 7/FD = 7), followed by hemorrhagic complications ($n = 7$; ASMO = 3/FD = 4) and progressive mass effect from giant aneurysms ($n = 7$; ASMO = 2/FD = 5).

The composite primary efficacy outcome was available for 275 of 278 patients in the RCT (98.9%). A poor primary efficacy outcome was found in 30.9% (43/139; 95% CI, 23.5%–39.4%) of patients with FD and 45.6% (62/136; 95% CI, 37.1%–54.3%) with ASMO, an absolute risk difference of 14.7%, (95% CI, 3.3%–26.0%) (relative risk, 0.68; 95% CI, 0.50–0.92; $P = .014$). Details of each component of the primary outcome are provided in Table 2. Attributing a good or a bad outcome when data were missing did not significantly modify the results. The primary outcome for per-protocol analyses is detailed in the Online Supplemental Data. As-attempted and as-treated analyses yielded similar results compared with intent-to-treat analyses, with patients undergoing FD having better primary efficacy outcomes than those undergoing ASMO ($P < .001$ for both).

The mean time of follow-up mRS recorded for the primary efficacy outcome was at 12.7 (SD, 7.4) months for ASMO and 12.2 (SD, 8.0) months for FD. The mean time of angiographic follow-up included in the primary efficacy outcome measure was 11.0 (SD, 5.3) months for patients randomly allocated to ASMO and 11.6 (SD, 5.7) months for patients randomly allocated to FD.

Prespecified subgroups of interest are shown in Fig 2, even though none of the interaction tests were significant. On the basis of this description, we observed that patients preselected for coiling with or without stent placement ($n = 199$) who were randomly allocated to FD had better outcomes, as did patients preselected for conservative treatment who randomly underwent

Subgroup Primary Outcome

	Interaction P-value	FD No.(%)	ASMO No.(%)		RR (95% CI)	P value
ASMO Choice	.0961					
Conservative management		4/12 (33.3%)	9/11 (81.8%)		0.41 (0.17-0.95)	.0378
Coiling w/wo stenting		27/99 (27.3%)	41/97 (42.3%)		0.65 (0.43-0.96)	.0305
Parent vessel occlusion		11/22 (50.0%)	9/23 (39.1%)		1.28 (0.66-2.47)	.4661
Surgical clipping		1/6 (16.7%)	3/5 (60.0%)		0.28 (0.04-1.91)	.1926
Rupture Status	.4643					
Ruptured		6/21 (28.6%)	14/26 (53.8%)		0.53 (0.25-1.14)	.1041
Unruptured		37/118 (31.4%)	48/110 (43.6%)		0.72 (0.51-1.01)	.0576
Aneurysm Location	.5290*					
Posterior Circulation		13/30 (43.3%)	17/31 (54.8%)		0.79 (0.47-1.33)	.3740
Anterior Circulation		30/109 (27.5%)	45/105 (42.9%)		0.64 (0.44-0.94)	.0211
Proximal carotid		23/74 (31.1%)	25/70 (35.7%)		0.87 (0.55-1.38)	.5560
Extradural		9/21 (42.9%)	6/14 (42.9%)		1.00 (0.46-2.18)	1.0000
Ophthalmic		14/53 (26.4%)	19/56 (33.9%)		0.78 (0.44-1.39)	.3970
Other carotid		1/12 (8.3%)	12/19 (63.2.0%)		0.13 (0.02-0.89)	.0374
Other anterior		6/23 (26.1%)	8/16 (50.0%)		0.52 (0.22-1.21)	.1311
Aneurysm Size	.1879					
< 10 mm		18/68 (26.5%)	19/65 (29.2%)		0.91 (0.52-1.57)	.7226
≥ 10 mm		25/71 (35.2%)	43/71 (60.6%)		0.58 (0.40-0.84)	.0038
FIAT - ITT		43/139 (30.9%)	62/136 (45.6%)		0.68 (0.50-0.92)	.0139

FIG 2. Subgroup analysis. Statistical analysis performed with data considered missing when the primary outcome was not available (*n* = 3). The *asterisk* indicates that the interaction *P* value for aneurysm location was calculated for the main division into anterior/posterior. w/wo indicates with or without; ITT, intention-to-treat; RR, relative risk.

FD (*n* = 23). The comparison of FD with PVO (*n* = 45) appeared to favor PVO, but it was inconclusive. Predefined subgroup analyses according to rupture status, size, and location showed better outcomes for unruptured, anterior circulation, and large (≥10 mm) aneurysms, while results were similar for <10-mm aneurysms and inconclusive for ruptured and posterior circulation aneurysms (Fig 2).

The primary efficacy outcome, modified to restrict the definition of a good angiographic outcome to complete occlusions, also showed the superiority of FD (*P* = .006) for all patients and for the same subgroups (Online Supplemental Data).

Secondary outcomes (successful intervention, perioperative complications, days of hospitalization, discharge disposition, mRS at discharge, and retreatment of the index aneurysm during follow-up) were similar in both groups (Online Supplemental Data). Details of angiographic results are also provided in the Online Supplemental Data. Complete occlusion of the aneurysm was more frequent with FD (*P* = .028) than with ASMO. When the definition of a good angiographic outcome included residual neck in addition to complete occlusion, the difference did not reach statistical significance (*P* = .09) (Online Supplemental Data).

Serious adverse events occurred in 28 patients with FD and 27 with ASMO. The distribution of serious and nonserious adverse events was not different between groups (*P* = .110). The only differences between groups were a nonsignificantly larger number of delayed (>1 month) serious events that occurred after FD (9 versus 3 events). Nonserious adverse events were more frequent with FD

(22 versus 9). Details are provided in the Online Supplemental Data. Details of poor clinical outcome at any time point are given for all patients in the Online Supplemental Data. The mRS scores for all patients in the RCT at 3 months and at the time of the primary efficacy outcome are detailed in the Online Supplemental Data.

DISCUSSION

FIAT is the first pragmatic trial showing improved efficacy outcomes with FD compared with other common management options. FIAT is also unique in showing that an endovascular innovation can be assessed in a randomized trial at the same time that it is introduced in clinical practice.[13,22] This change is an important breakthrough, for neurovascular devices have so far been approved on the basis of industry-led single-arm case series of ~100 patients selected for regulatory approval purposes.[2,23,24] This is problematic, for clinical usage typically expands beyond the initial regulatory indications without reliable evidence that the innovation improves patient outcomes.[25]

FIAT successfully addressed the multiple challenges that confront trials that assess the safe introduction of promising-but-potentially risky surgical innovations. One challenge is the diversity of patients, aneurysms, and clinical presentations. Before the availability of FD, these patients were treated using various ASMOs selected according to clinical presentation, individual patient anatomy, aneurysm location and morphology, local practice patterns, and individual preferences.[10] The goal of treatment also varies, from relief of symptoms of

mass effect to the prevention of life-threatening aneurysm ruptures in asymptomatic individuals. An explanatory attitude, looking for a signal that the innovation can work, fearing to lose that signal due to the noise associated with heterogeneity, might have called for multiple trials, each comparing FD in homogeneous patients eligible for only a single alternative treatment. However, this approach would not have addressed our main concern, which is whether FD actually improves patient outcomes in routine practice.[26]

FIAT is also the prototype care trial.[13] The guiding principle of the design is that patients are better protected when promising-but-unproven innovations are offered within a carefully controlled research context. This principle means that each item of the trial protocol must be reviewed to best protect the medical interest of participants.[13,22] Care trials are as inclusive as possible; protocols are flexible and allow the use of the treatment the patient would have otherwise received. The comparator intervention was prespecified before stratified randomized allocation, allowing valid comparisons within subgroups.

Care trials are fully integrated into clinical practice, and involve no extra risks, tests, visits, or cost compared with routine care. Although this design allowed us to conduct the trial without the support of industry or research agencies, the lack of funding discouraged many centers from participating. The data were collected by normal care personnel at the time of routine clinical follow-up visits. The main drawback of the approach, when rigorously applied, is that blinding becomes almost impossible. To mitigate that problem, we used a standardized, simplified mRS questionnaire[18] and dichotomized results for a more difficult end point, death or dependency, which is more resistant to bias. This approach has been shown to be reliable.[27]

The primary end point of the trial was a composite that attempted to capture in 1 judgment the comparative value of treatment in terms of safety and efficacy. This outcome combined clinical results (an independent functional score [mRS <3], which is the scale most frequently used in stroke trials) and the absence of clinical events signaling treatment failure during follow-up (such as aneurysm rupture, progressive mass effect, or retreatment of the index aneurysm). To account for the relatively short follow-up compared with lifetime protection against ruptures, which is the goal of treatment in many patients, the primary outcome included an angiographic result: complete or near-complete occlusion of the aneurysm. Angiographic outcomes are routinely used in practice to judge the success of therapy.[28] They are also the most common primary outcome of aneurysm trials.[20,28-33] Residual aneurysm was used to judge treatment failure because this category has been shown to be repeatable and its clinical significance is more constant across various raters, imaging modalities, and treatments.[20,21] The exploratory analyses we performed showed that using complete or near-complete occlusion as the angiographic outcome did not change the conclusions.

The overall morbidity and mortality of patients treated in FIAT are relatively high compared with these outcomes in other endovascular trials.[34-36] However, those comparisons are not valid because aneurysms considered for FD in FIAT were typically larger, more frequently had symptoms of mass effect, and many were difficult to treat by any and all methods. The primary safety outcome for all patients who received FD (26/209 or 12%;

Online Supplemental Data) was at the upper limit of our initial estimate (10%) but similar that in to another randomized trial that compared FD with stent-assisted coiling.[11] In the Parent Artery Reconstruction for Large or Giant Cerebral Aneurysms Using a Tubridge Flow Diverter (PARAT) trial, the rates of death or stroke related to target vessels at 1-year follow-up were 14% and 17% in the stent-assisted coiling and FD groups, respectively.[11] Delayed complications, such as aneurysm ruptures, parenchymal hematomas at a distance from the aneurysm, and strokes from stent thrombosis were infrequent (10/209 or 4.8% of all patients having undergone FD in FIAT; Online Supplemental Data), but they remain a concern if FD is to be widely used.

The trial was all-inclusive, but not all patients with aneurysms were considered for FD, and results may not apply to all patients. To examine how study results could apply in clinical decision-making, one must examine prespecified subgroups of patients, even if the interaction tests were not statistically significant. The interaction test examines the potential influence of a variable on a single relative treatment effect, an implausible assumption in this trial comparing FD with as widely different options as conservative management and PVO. Nevertheless, subgroup results should always be interpreted with caution.

Examining the prespecified subgroups defined according to the comparator ASMO showed that FD was more effective than coiling with or without stent placement, but comparisons with PVO or surgical clipping were too few to draw firm conclusions.

Because of the pragmatic nature of the trial, conservative management was a potential prespecified ASMO (actually selected in 23 or 8% of patients in the RCT). This design choice may seem to unfairly favor FD. However, the alternative, to exclude these patients from the RCT, would have deprived the trial of the capacity to show this important advance provided by FD, ie, the ability to treat patients who otherwise could not be treated.

For prespecified aneurysm characteristics, FD was shown to be superior in the treatment of large, unruptured intradural carotid aneurysms (>10 mm), confirming the results of a previous trial.[11] For the initially approved regulatory indications for the use of FD (proximal carotid aneurysms), results were neutral, for they pull in opposite directions. Many large or giant extradural carotid aneurysms were treated with PVO, a treatment subgroup that was superior to FD (but not significantly) (Fig 2). Another trial showed FD to be less effective (but safer) than surgical occlusion and bypass in the treatment of complex anterior circulation aneurysms.[12] Surgical bypass was not used in FIAT, even in combination with PVO, and the RCT included only those patients with a circle of Willis that allowed safe carotid occlusion without bypass. PVO remains a good option for these selected patients.[37]

Posterior circulation aneurysms have been shown in observational studies to have worse outcomes after FD than anterior circulation aneurysms, but FIAT randomized results show that ASMOs did not perform better for these difficult lesions (Fig 2).[25]

There are a priori concerns with the use of antiplatelet regimens that come with the use of FD in patients with SAH from a recently ruptured aneurysm.[38] Too few patients with SAH were included in FIAT for conclusions to be drawn about FD use in these patients.

For the most frequently encountered small (<10 mm), unruptured, asymptomatic, intradural aneurysms, the primary efficacy

outcome was similar for patients treated with FD or ASMO. Only by looking at the rate of complete occlusion in exploratory analyses can a signal possibly favoring FD be detected (Online Supplemental Data). FIAT results are in accordance with performance goals for FD of small and medium aneurysms that have recently been proposed (morbidity/mortality in 7.8% of patients [4.8%–11.4%]).[39] Subgroup safety data for coiling with or without stent placement (3%; 95% CI, 0%–8.5%) and for the corresponding stratified patients with FD (5%; 95% CI, 1.6%–11.4%) were comparable in FIAT, but a larger RCT would be needed for the ongoing concern of delayed complications with FD related to antiplatelet regimens and delayed stent thrombosis. Some believe that a 5%–8% risk may already be too high to justify the preventive treatment of small unruptured aneurysms.[9] The pertinent question regarding small asymptomatic aneurysms is whether they should even be treated at all.[40] A pragmatic RCT has recently been launched to address this question.[41]

There are limitations to this study: Only 3 Canadian centers participated, limiting the generalizability of results. The recruitment period had to be increased to nearly 10 years, during which the indications for FD are likely to have changed. FIAT is the largest RCT on FD so far, but the number of patients remains small. On final analysis, safety results include the possibility of harm or benefit compared with other management options. Prerandomization resulted in 24 crossovers (8.6%) that dilute the contrast between groups. An aneurysm for which FD is considered a promising treatment is a vague definition that may be differently interpreted from one clinician to another and that may also change with time and experience. Clinical outcome assessment and core lab adjudications could not be masked to treatment allocation. Trial results were mainly driven by angiographic results, and the hard clinical outcome (death or dependency) accounted for a relatively small number of poor outcomes in both groups (13 versus 10 patients, including 9 versus 5 deaths). Potential bias from lack of blinding of mRS clinical assessors should not have significantly affected the results. The 12-month follow-up period was relatively short; too short to evaluate the effects of treatment on aneurysm rupture. In addition, this follow-up may not have given enough time for some FD-treated aneurysms to become occluded or for some recurrences after coiling to become apparent.[42]

CONCLUSIONS

For patients with mostly unruptured, large, anterior circulation (carotid) aneurysms, FD was more effective than ASMO in terms of angiographic outcome. More randomized trials are needed to assess safety.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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