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ORIGINAL RESEARCH

# Flow diversion for the treatment of distal circulation aneurysms: A randomized comparison

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Flow diversion (FD) has expanded beyond initial indications (proximal carotid artery aneurysms) to include distal circulation aneurysms (on the anterior, middle, or posterior cerebral arteries). Our objective was to examine results obtained from aneurysms in these locations in the Flow Diversion in the Treatment of Intracranial Aneurysms Trial (FIAT) which compared FD with alternative standard management options (ASMO).

**MATERIALS AND METHODS:** FIAT was an all-inclusive parallel-group 1:1 randomized study comparing FD with one of 4 ASMOs (coiling +/- stenting, parent vessel occlusion (PVO), clipping, or observation, pre-specified by clinical judgment). The primary safety outcome was death or dependency (mRS >2) at 3 months. The composite primary outcome was "treatment failure," defined as initial failure to treat the aneurysm; aneurysm rupture or retreatment during follow-up; death or dependency (mRS>2); or angiographic residual aneurysm adjudicated by independent core laboratory at 12 months. This subgroup analysis was not prespecified and there was no blinding.

**RESULTS:** Of the 323 patients in FIAT, 46 (14%) with distal circulation aneurysms were randomly allocated: 23 to FD and 23 to ASMO (coiling +/- stenting (16 patients), PVO (1), clipping (3), and observation (3)). Death or dependency at 3 months occurred in one patient (allocated ASMO). Treatment failures occurred in 6/23 FD-treated patients (26.1%; 95%CI: 12.6%-46.5%) compared to 11/22 patients treated with ASMO (50.0%; 95%CI: 30.7%-69.3%; RR=0.52, [0.23-1.17]; P=0.13). Serious adverse events were similar.

**CONCLUSIONS:** Distal circulation aneurysms treated with FDs in FIAT showed an encouraging trend, but this analysis was underpowered. Further randomized trials are needed.

**ABBREVIATIONS:** ASMO = Alternative standard management options; FD = Flow Diversion; FIAT = Flow Diversion in the Treatment of Intracranial Aneurysms Trial; PVO = Parent Vessel Occlusion; mRS = modified Rankin Scale

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## SUMMARY SECTION

**PREVIOUS LITERATURE:** Flow diversion (FD) is increasingly used for treating intracranial aneurysms, including those located in the distal circulation, with observational studies and reviews suggesting safety and efficacy. However, aneurysm occlusion rates and complications are variable, and no randomized studies have compared FD to standard management options.

**KEY FINDINGS:** This randomized comparison suggests FD may be a promising treatment for distal circulation aneurysms compared to coiling with or without stenting, but the study was underpowered to provide conclusive evidence.

**KNOWLEDGE ADVANCEMENT:** The study suggests that future randomized trials may show the clinical benefits of using flow diversion in distal circulation aneurysms.

## INTRODUCTION

Flow diversion (FD) was initially approved by the US Food and Drug Administration for the treatment of unruptured large and giant aneurysms of the proximal segments of the carotid artery in 2011.[1] Aided by the development of smaller flow diverters delivered by smaller catheters, the use of FD has since expanded to aneurysms of all sizes and locations.[2,3] This includes treatment for distal aneurysms, here defined as aneurysms arising from the middle, anterior or posterior cerebral arteries. There may be specific risks to the use of FD in such locations, such as more difficult navigation, and coverage of perforators or bifurcation branches with risks of delayed occlusion. The available data on the use of FD in these locations has shown promising results, with complete occlusion rates ranging from 67%[4] to 96%[5] and morbidity rates from 3%[6] to 11%,[7] but it is mostly limited to cases series, without proper comparison with standard alternative management options.[4–13] Thus, the best treatment of distal aneurysms remains uncertain.

The Flow Diversion in Aneurysm Treatment (FIAT) trial was recently published.[14] The trial was pragmatic and included patients with distal circulation aneurysms. FIAT randomly allocated FD 1:1 with an alternative standard management option (ASMO): i) coiling with or without stenting, ii) surgical clipping,

iii) PVO or iv) observation. In this post-hoc analysis, we detail the results of FD compared to alternative managements in patients with distal circulation aneurysms.

## MATERIALS AND METHODS

This report was prepared in the spirit of the CONSORT recommendations,[15] but this subgroup comparison is not a stand-alone trial. The study protocol (Clinical trial.gov: NCT01349582) was published in 2011[16] and final results were reported in 2022.[14]

Briefly, FIAT was an investigator-led, pragmatic randomized care trial conducted in 3 Canadian centers (Montreal, Edmonton, and Ottawa). FIAT included all adult patients with an intracranial aneurysm and for whom flow diversion was considered. 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.

Concealment of randomized allocation was assured through a web-based platform. Before randomization, the treating physicians had to first choose which of the following five alternative management options would be carried out if the allocation fell to ASMO: 1 = coiling (with or without stenting); 2 = parent vessel occlusion (PVO); 3 = surgical clipping; 4 = conservative management or 5 = FD registry (non-randomized allocation).

FIAT 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.[17] The target number of patients to be recruited was reached in July 2020. 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. Data entry was locked on June 1, 2021 without knowledge of outcome results.

### *Patients*

We report the results for all patients with distal circulation aneurysm (i.e. aneurysms located on the middle, anterior or posterior cerebral arteries) included in FIAT from inception in February 2011 to completion in June 2021.

### *Interventions*

Standard local procedures were followed. Any intra-arterial flow-diverting stent (but not intra-saccular flow disruptors such as the WEB) were permitted. Testing for platelet inhibition was not required per protocol; antiplatelet and anticoagulation regimens were according to routine practice at each site. Follow-up tests and visits, as clinically indicated, included neurological examinations, brain imaging studies, and a functional assessment according to the mRS score at discharge, 1 month, and 3–12 months, and angiography at 3–12 months. Data capture and management were completed through secure servers (MedSciNet, Sweden) in compliance with good clinical practice requirements. Case report forms were simple, and limited data were collected to facilitate completion by normal care personnel. No financial compensation was provided to participating centers.

### *Outcome measures and Blinding*

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 of outcomes was used to classify each patient: death > mRS 3–5 (from any cause, including aneurysm rupture or progressing mass effect, with the mRS assessment made at the time of follow-up imaging) > aneurysm rupture during follow-up > retreatment during follow-up > initial treatment failure > residual aneurysm at imaging follow-up (12 months) as adjudicated by an independent core lab using a previously validated 3 category system (complete occlusion, residual neck, residual aneurysm).[18,19] The residual aneurysm category was used to adjudicate treatment failure for the primary outcome analysis, and the complete occlusion category was used for exploratory analyses. The presence of various endovascular 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 scores at discharge, 3 months and 12 months after treatment; immediate post-procedural degree of occlusion; perioperative complications (ischemic and hemorrhagic); angiographic (invasive or noninvasive imaging) results at 3 and 12 months; length of hospital stay (number of days); discharge disposition (home, other hospital, rehabilitation facility, or death); any new stroke, neurological symptom or sign during follow-up; and retreatment of the index aneurysm at any time. Patients, interventionalists, and outcome assessors were not masked to treatment assignment, which was deemed not feasible.

### *Statistical analysis*

There was no power calculation for this subgroup analysis. The overall FIAT trial was powered (80%) to show a 15% increase (from 75% to 90%; alpha error 5%; 224 patients plus losses and crossovers for a total of 250 patients) in the incidence 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).

Descriptive statistics on demographic variables and pre-operative data are provided to compare the two groups at baseline. Means, standard deviations, medians and ranges are presented for quantitative variables and frequency tables for categorical variables. Primary safety and efficacy outcomes are described using percentages and 95% confidence intervals. The intent-to-treat analyses for the primary efficacy hypothesis were done on available observations. The relative risks (and 95% confidence intervals) were estimated using a generalized estimating equation (GEE) with a binomial distribution and a log-link function.

The primary outcome measures were compared using Chi-square tests. Subgroup results according to aneurysm size (< 10 or ≥10 mm), location (anterior, middle, and posterior cerebral artery) and according to selected ASMO are reported. 'As-treated' analyses only included patients in whom FD or ASMO were 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) has been used as the criterion for a good angiographic result. Analyses were using SAS software version 9.4 and SPSS version 26 with a significance level of 5%. There was no correction to account for the multiplicity of analyses.

## RESULTS

Patients included in this subgroup analysis are shown in the flowchart (Fig 1). There were 51 patients with distal circulation aneurysms, or 15.8% of the 323 patients enrolled in FIAT. Five patients (9.8%) deemed ineligible for standard options were included in the registry and received FD; 46 patients (90.2%) were randomly allocated to FD (n=23) or to ASMO (n=23). The ASMO selected prior to randomization was coiling (with or without stenting) in 32, PVO in 3, surgical clipping in 7 and observation in 4 patients. The treatments actually performed in patients allocated ASMO are detailed in Fig 1.

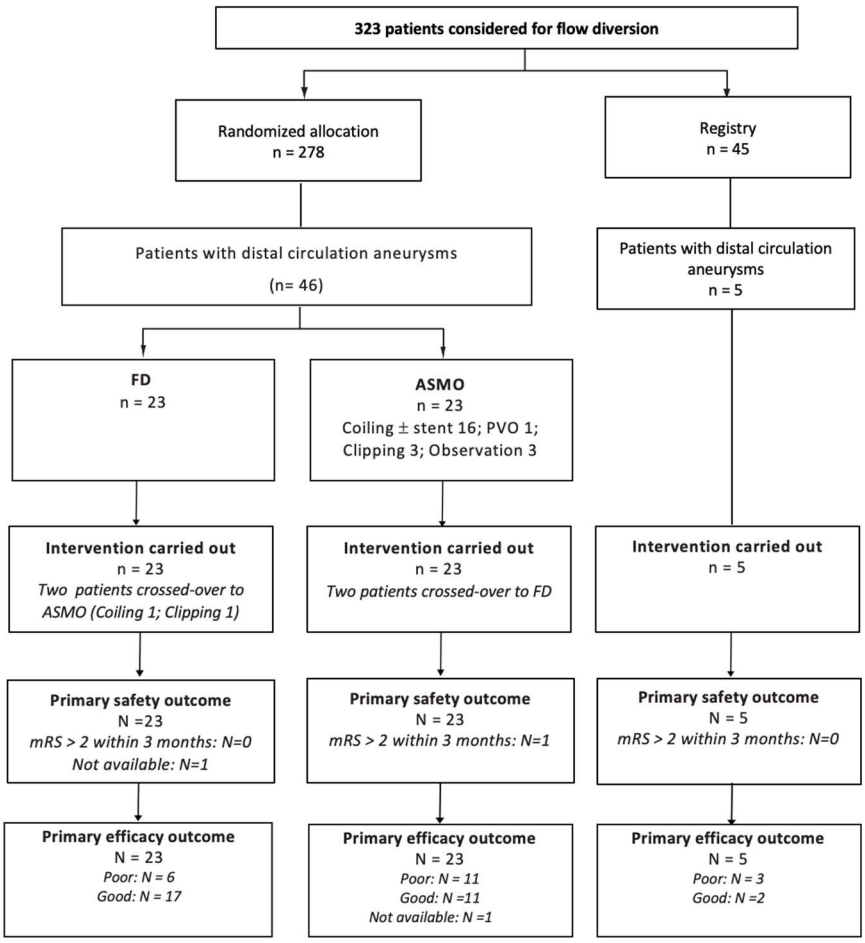



**FIG 1.** Flowchart of patients. FD: flow diversion, ASMO: alternative standard management options; PVO: parent vessel occlusion; mRS: modified Rankin Scale

Patient and aneurysm characteristics for each group are presented in Table 1. Many patients had MCA aneurysm (34/46, 73.9%). There were few patients with posterior cerebral artery (n=6) or ruptured aneurysms (n=8), but they were not balanced between groups: all were randomly allocated to ASMO (Table 1).

**Table 1:** Patient and index aneurysm characteristics.

| Characteristics | FD (n = 23) | ASMO (n = 23) | Registry (n = 5) |
|---|---|---|---|
| Patients | | | |
| Age (mean) (SD) (yr) | 57.4 (12.4) | 57.3 (12.7) | 56.8 (14.4) |
| Female (No) (%) | 17 (73.9) | 14 (60.9) | 4 (80.0) |
| Pre-treatment mRS score (No) (%) | | | |
| 0 | 15 (65.2) | 11 (47.8) | 2 (40.0) |
| 1 | 7 (30.4) | 8 (34.8) | 2 (40.0) |
| 2 | 0 | 1 (4.3) | 0 |
| 3 | 1 (4.3) | 2 (8.7) | 1 (20.0) |
| 4 | 0 | 1 (4.3) | 0 |
| Presentation | | | |

| | | | |
|---|---|---|---|
| Symptomatic – mass effect | 5 (21.7) | 4 (17.4) | 3 (60.0) |
| Symptomatic – SAH | 0 | 8 (34.8) | 0 |
| Asymptomatic | 18 (78.3) | 11 (47.8) | 2 (40.0) |
| Index aneurysm location (No) (%) | | | |
| MCA | 20 (87.0) | 14 (60.9) | 4 (80.0) |
| Proximal M1 | 1 (4.3) | (2 (8.7) | 1 (20.0) |
| MCA bifurcation | 14 (60.9) | 12 (52.2) | 2 (40.0) |
| Distal to MCA bifurcation | 5 (21.7) | 0 | 1 (20.0) |
| ACA | 3 (13.0) | 3 (13.0) | 0 |
| AComm | 0 | 2 (8.7) | 0 |
| ACA distal to AComm | 3 (13.0) | 1 (4.3) | 0 |
| PCA | 0 | 6 (26.1) | 0 |
| Median index aneurysm diameter (mm) (SD) [range] | 14.0 (12.7) [5 – 19] | 11.1 (8.8) [4 - 16] | 19.6 (13.8) [5 – 17.5] |
| < 10 mm (No) (%) | 13 (56.5) | 12 (52.2) | 1 (20.0) |
| 10-24 mm (No) (%) | 7 (30.4) | 8 (34.8) | 3 (60.0) |
| ≥ 25, n (%) | 3 (13.0) | 3 (13.0) | 1 (20.0) |
| Mean neck size (mm), (SD); [range] | 4.7 (2.0) [3 – 5.5] | 4.6 (3.0) [3 - 6] | 3.5 (0.7) [3.25 – 3.75] |
| < 4 mm, n (%) | 7 (30.4) | 9 (39.1) | 1 (20.0) |
| ≥ 4, n (%) | 13 (56.5) | 12 (52.2) | 1 (20.0) |
| Not measurable | 3 (13.0) | 2 (8.7) | 3 (60.0) |

FD: flow diversion; ASMO: alternative standard management options; mRS: modified Rankin scale; MCA: Middle cerebral artery; ACA: Anterior cerebral artery; AComm: Anterior communicating; PCA: Posterior cerebral artery.

There were two crossovers from ASMO to FD (one patient assigned to conservative treatment and one to coiling) and two cross-overs from FD to ASMO (one to coiling and one to surgery), all based on clinical judgment (Fig 1).

The composite primary efficacy outcome was available for 45/46 patients (one patient with a 17-mm MCA bifurcation aneurysm allocated to ASMO was lost to follow-up). A poor primary efficacy outcome (treatment failure) was reached in 6/23 FD patients (26%, 95%CI:13%-46%) as compared to 11/22 ASMO patients (50%, 95%CI:31%-69%) (RR = 0.52, 95%CI [0.23-1.17]; p=0.13). Details of each component of the primary outcome for all patients are provided in Table 2. Dichotomized results for patients with ruptured and unruptured aneurysms in the ASMO group are provided in Online Supplemental Data.

**Table 2:** Primary efficacy outcomes.

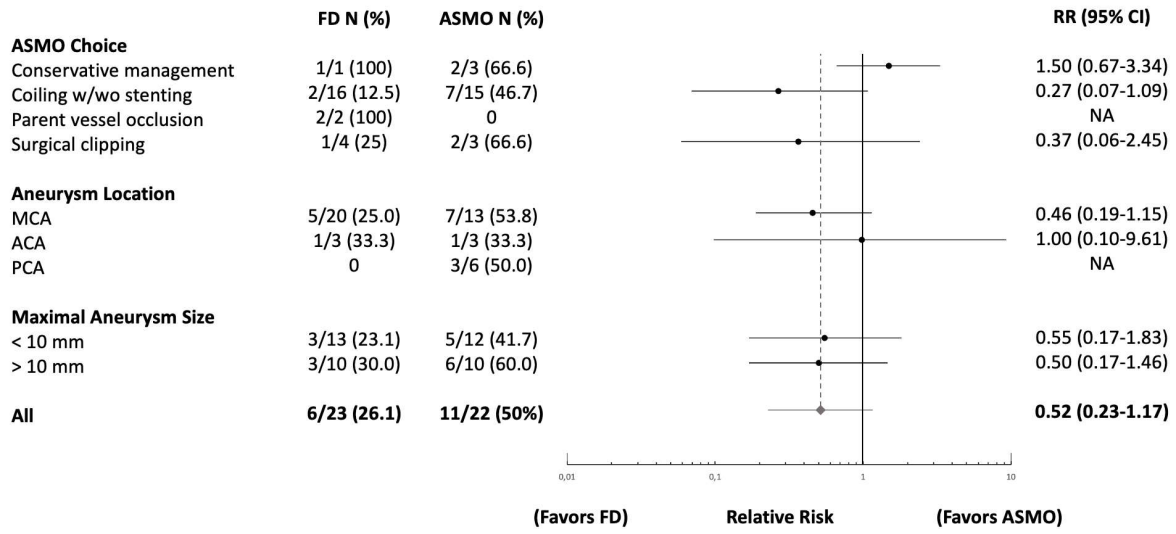
| Intent to Treat Analysis 1-year Outcome* | FD (n = 23) | ASMO (n = 23) | Registry (n = 5) |
|---|---|---|---|
| Treatment Failure (composite) (No) (%) | 6 (26.1) | 11 (47.8) | 3 (60.0) |
| Clinical | | | |
| mRS 6 | 1 (4.3) | 1 (4.3) | 0 |
| mRS 3-5 | 0 | 0 | 0 |
| SAH from aneurysm rupture | 0 | 0 | 0 |
| Retreatment | 1 (4.3) | 1 (4.3) | 2 (40.0) |
| Immediate failure | 1 (4.3) | 2 (8.7) | 0 |
| Angiographic | | | |
| Residual aneurysm (core lab) | 3 (13.0) | 7 (30.4) | 1 (20.0) |
| Missing primary outcome | 0 | 1 (4.3) | 0 |

FD: flow diversion; ASMO: alternative standard management options

* RR = 0.52, 95%CI [0.23-1.17]; p=0.13

Most failures were angiographic (n = 10/17; 7 ASMO and 3 FD) (Table 2). Poor clinical outcomes (death, mRS 3-5, SAH from aneurysm rupture, retreatment and immediate treatment failure) are detailed in Online Supplemental Data.

Results for various subgroups are illustrated in the forest plot (Fig 2).




PVO: parent vessel occlusion; FD: flow diversion.

**FIG 2.** Subgroup analysis (intent-to-treat).

The primary safety outcome, death or dependency at 3 months, occurred in 1 of 23 patients (4%; 95%CI:1%-21%) randomly allocated ASMO and none of the 22 patients allocated FD (0%;95%CI:0%-15%). This 56-year-old patient with a ruptured 25-mm MCA aneurysm experienced a symptomatic stroke after surgery, resulting in an mRS score of 4 at 3 months. By the 1-year follow-up, his mRS score had improved to 2.

Secondary outcomes (days of hospitalization, discharge disposition, mRS at discharge, retreatment of index aneurysm during follow-up) were similar for both groups (Online Supplemental Data). Angiographic results were not significantly different. Complete aneurysm occlusion was found in 15/23 patients (65%; 95%CI:45%-81%) randomly allocated to FD and in 10/22 patients (45%; 95%CI:27%-65%) allocated to ASMO (RR 1.43; 95%CI [0.83-2.48]; P=0.24) (Online Supplemental Data).

Serious adverse events occurred in 2 of 23 (9%; 95% CI:2%-27%) patients randomly allocated FD and 4 of 23 (17%; 95% CI:7%-37%) allocated ASMO. Non-serious adverse events occurred in 6/23 (26%; 95% CI:13%-46%) randomly allocated to FD and 1/23 (4%; 95%CI:1%-21%) patients allocated ASMO. Adverse events are detailed in Online Supplemental Data.
As-treated analyses were similar to intent-to-treat analyses. The primary outcome (treatment failure) occurred in 6/23 FD patients (26%; 95%CI:13%-46%) as compared to 11/22 ASMO patients (50%; 95%CI:31%-69%) (RR = 0.52, 95%CI [0.23-1.17]; P=0.13). Details of each component of the primary outcome are provided in Online Supplemental Data.

## DISCUSSION

This randomized comparison showed that flow diversion may be a promising option in the treatment of distal circulation aneurysms, as compared to coiling with or without stenting (the most frequent comparator management option), but the study is too small to be conclusive.

There is an increasing trend toward the use of flow diversion (FD) for the treatment of most unruptured intracranial aneurysms, and distal circulation aneurysms are no exception.[20] This trend is supported by numerous observational studies and systematic reviews, all suggesting that FD may be safe and effective in these locations, but there are large variations in aneurysm occlusion, complications and morbidity rates, and few if any randomized comparisons with standard management options.[4-14, 21-23] The FIAT trial[14] demonstrated that FD offers better angiographic outcomes than pre-selected alternative treatments, but results were mainly driven by large carotid aneurysms. No specific analysis was conducted on patients with distal circulation aneurysms.

Most patients in the current study had MCA aneurysms (34/46, 73.9%), with coiling being the most common ASMO selected (32/46, 69.6% overall, and 24/34, 70.6% for MCA cases). As a result, the overall findings are primarily influenced by this subgroup comparison. There were too few patients treated by surgical clipping, PVO, or conservative management, and too few patients with other kinds of aneurysms to draw conclusions, highlighting the need for further randomized trials.

The randomization process did not balance the small number of patients with ruptured aneurysms between the 2 groups, but because ruptured or unruptured aneurysms treated by coiling had similar rates of primary outcomes and SAEs, we believe this imbalance did not impact results.

In terms of safety, serious adverse events were similar, but given the small number of patients, no definitive conclusions can be drawn.

FIAT was a pragmatic care trial, a type of clinical study that aims to evaluate medical interventions in a real-world clinical setting. Unlike explanatory trials, which are conducted in controlled environments to test hypotheses under ideal conditions, care trials study normal care delivered in real-world conditions. Care trials can rigorously test a new intervention such as flow diversion within the context of routine care, ensuring that any potential benefits and risks are clearly understood before the intervention is adopted as standard treatment. Care trials are designed in the best medical interests of participating patients. They follow specific rules in their design. They introduce no additional tests or risks beyond what is already proven to be beneficial in routine care. There are no extra interventions added solely for the purpose of the trial. Outcomes are predefined, meaningful, and resistant to bias, while follow-up visits and tests are part of regular patient management. Because care trials mirror everyday clinical practice, selection criteria are inclusive, to assist most current patients facing the clinical problem.[24,25] In the FIAT trial, patients were eligible to participate regardless of aneurysm location (including distal aneurysms), clinical presentation, or alternative treatment options. Because conservative management for some aneurysms is an appropriate management option, it had to be included as a potential comparator.[26] Of course, patients allocated to observation are less likely to suffer immediate complications and are also more likely to have a residual aneurysm at one year, as compared to flow diversion. In a care trial such as FIAT, the results for all subgroups, including conservatively managed patients, are transparently reported. That said, the subgroup of conservatively managed distal aneurysms in FIAT had little effect on the overall results, as only 4 patients (8.7%) had observation as the chosen comparator (Fig 2).

This study has multiple limitations. It was a non-pre-specified underpowered subgroup analysis, so the findings should be considered exploratory. Only few centers participated and the total number of patients was small. There were imbalances in the number of patients with posterior circulation and ruptured aneurysms between the two groups. Clinical outcomes were not evaluated in a blind fashion. The FIAT recruitment period spanned nearly a decade, during which devices, techniques, and expertise have changed. The 12-month follow-up period might not have been sufficient to capture all clinical consequences, such as recurrences, retreatments and any associated morbidity. At the time of the FIAT trial design, intrasaccular flow diverting devices were not available; this option was not included in the alternative standard management option to be pre-specified prior to randomization.

Nevertheless, this study may contribute to future meta-analyses or serve as a hypothesis for a future trial which may ultimately offer a definitive answer regarding the best treatment. Meanwhile, conducting a care trial dedicated to distal circulation aneurysms may help regulate practice under uncertainty. A care trial optimizes clinical practice by giving each patient a 50% chance of receiving either the innovative treatment or standard care, thus balancing the risks associated with receiving an inferior treatment.[24]

## CONCLUSIONS

This randomized comparison between FD and ASMO in patients with distal circulation aneurysms provides valuable data, but the study was underpowered. Further randomized trials are necessary.


## ACKNOWLEDGMENTS

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SUPPLEMENTAL FILES

**Online Table 1:** Primary Efficacy Outcomes: Dichotomized results of patients with ruptured (SAH+) and unruptured (SAH-) in the ASMO group.

| Intent to Treat Analysis 1-year Outcome* | FD (n = 23) | ASMO (n = 23) | ASMO SAH + (n= 8) | ASMO SAH – (n = 15) |
|---|---|---|---|---|
| Treatment Failure (composite) (No) (%) | 6 (26.1) | 11 47.8) | 4 (50.0) | 7 (46.7) |
| Clinical | | | | |
| mRS 6 | 1 (4.3) | 1 (4.3) | 1 (12.5) | 0 |
| mRS 3-5 | 0 | 0 | 0 | 0 |
| SAH from aneurysm rupture | 0 | 0 | 0 | 0 |
| Retreatment | 1 (4.3) | 1 (4.3) | 0 | 1 (6.7) |
| Immediate failure | 1 (4.3) | 2 (8.7) | 2 (25) | 0 |
| Angiographic | | | | |
| Residual aneurysm (core lab) | 3 (13.0) | 7 (30.4) | 1 (12.5) | 6 (40) |
| Missing primary outcome | 0 | 1 (4.3) | 0 | 1 (6.7) |

FD: flow diversion; ASMO: alternative standard management options, SAH: subarachnoid haemorrhage

**Online Table 2:** Details of poor clinical outcomes

| Age, Sex | Aneurysm | 1-year mRS | Days since procedure | Details | Outcome |
|---|---|---|---|---|---|
| **Flow diversion** | | | | | |
| 63, F | 20mm symptomatic MCA distal to bifurcation aneurysm | 6 | 511 | Fatal arterial rupture during FD re-treatment of recurrence | Death |
| 33, M | 23mm asymptomatic MCA distal to bifurcation aneurysm | 1 | 104 | Re-treatment with a second FD | Retreatment |
| 50, F | 5mm asymptomatic ACA distal to AComm aneurysm | LFU | 0 | Failure of catheterization | Immediate treatment failure |
| **ASMO** | | | | | |
| 52, M | 12mm symptomatic PCA aneurysm | 3 | 270 | Retreatment with a second stent and coils | Retreatment |
| 68, F | 2mm ruptured AComm aneurysm | 6 | 442 | Unrelated death (lung cancer) | Death |
| 47, F | 3mm ruptured posterior PCA aneurysm | 0 | 189 | Failure of treatment with coiling. Successful treatment with FD 5 months later | Immediate treatment failure |
| 63, F | 4mm ruptured MCA bifurcation aneurysm | 0 | 0 | Treatment with FD after failure of treatment with coiling | Immediate treatment failure |
| **Registry** | | | | | |
| 68, F | 22mm symptomatic MCA distal to bifurcation aneurysm | 2 | 464 | Surgical debulking | Retreatment |
| 56, F | 40 mm symptomatic MCA bifurcation aneurysm | 0 | 144 | Retreatment with a second FD and coils | Retreatment |

FD: flow diversion; ASMO: alternative standard management options, mRS: modified Rankin Scale; LFU: lost to follow-up; MCA: middle cerebral artery; ACA: anterior cerebral artery; PCA: posterior cerebral artery, AComm: anterior communicating.

**Online Table 3:** Secondary outcomes

| Secondary outcomes | FD (n = 23) | ASMO (n = 23) |
|---|---|---|
| Hospitalization | | |
| Number of patients hospitalized for >3 days, n (%) | 3 (13.0) | 5 (21.7) |
| Discharge location n (%) | | |
| Home | 22 (95.7) | 19 (82.6) |
| Other than home | | |
| Other hospital | 0 | 1 (4.3) |
| Rehabilitation center | 1 (4.3) | 3 (13.0) |
| Death | 0 | 0 |
| mRS at discharge, n (%) | | |
| 0 | 19 (82.6) | 13 (56.5) |
| 1 | 2 (8.7) | 7 (30.4) |
| 2 | 2 (8.7) | 1 (4.3) |
| 3 | 0 | 1 (4.3) |
| 4 | 0 | 1 (4.3) |
| 5 | 0 | 0 |
| 6 | 0 | 0 |
| 1 year mRS, n (%) | | |
| 0 | 16 (69.6) | 11 (47.8) |
| 1 | 4 (17.4) | 8 (34.8) |
| 2 | 1 (4.3) | 2 (8.7) |
| 3 | 0 | 1 (4.3) |
| 4 | 0 | 0 |
| 5 | 0 | 0 |
| 6 | 1 (4.3) | 1 (4.3) |
| Not available | 1 (4.3) | 0 |
| Mean time of 1-year mRS assessment: months (SD) | 12.0 (9.4) | 10.3 (4.8) |
| Morbidity and mortality at 1 year (mRS>2), n (%) | 1 (4.3) | 2 (8.7) |
| Re-treatment of index aneurysm during follow-up, n (%) | 2 (8.7) | 2 (8.7) |
| Angiographic outcome at one year (core lab) | | |
| Complete occlusion, n (%) | 15 (65.2) | 10 (43.5) |
| Residual neck, n (%) | 2 (8.7) | 2 (8.7) |
| Residual saccular aneurysm, n (%) | 6 (26.1) | 10 (43.5) |
| Not available, n (%) | 0 | 1 (4.3) |
| Mean time of 1-year imaging assessment: months (SD) | 9.6 (5.6) | 11.6 (6.0) |

FD: flow diversion; ASMO: alternative standard management options, mRS: modified Rankin Scale.

**Online Table 4:** Angiographic results in intent-to-treat analyses

| **Intent to Treat**<br>**Angiographic outcome at one year** | **FD** | **ASMO** | **RR (95%CI)** |
|---|---|---|---|
| Residual aneurysm vs. others | 6/23 | 10/22 | 0.57 (0.25-1.31) |
| Complete occlusion vs. others | 15/23 | 10/22 | 1.43 (0.83-2.48) |

**Online Table 5:** Adverse events (intent-to-treat analysis)

| | FD (n = 23) | ASMO (n = 23) | Any FD* (n = 32) |
|---|---|---|---|
| **Serious Adverse Events, n (%)** | **2 (8.7)** | **4 (17.4)** | **3 (9.4)** |
| Ischemic | 0 | 2 | 0 |
| Hemorrhagic | 1 | 0 | 1 |
| Epilepsy | 1 | 0 | 1 |
| Mass effect | 0 | 0 | 1 |
| Unrelated | 0 | 2 | 0 |
| **Non-serious Adverse Events, n (%)** | **6 (26.1)** | **1 (4.3)** | **7 (21.9)** |
| Imaging finding | 3 | 1 | 4 |
| TIA | 3 | 0 | 3 |
| **Total, n (%)** | **8 (34.8)** | **5 (21.7)** | **10 (31.2)** |

SAE, serious adverse event; AE, adverse event.

* Any flow diverter includes: All patients randomly allocated FD (n=23), patients with distal aneurysms who received FD in the registry (5), and patients of the ASMO group who received FD at any time (2 cross-overs initially and 2 retreatments after the primary efficacy outcome was reached).

**Online Table 6:** Details of serious adverse events

| Aneurysm location | Patient age | Aneurysm Size | Neck width | Procedure carried out | Event | 1-year mRS > 2 | Adverse event | Reason for SAE |
|---|---|---|---|---|---|---|---|---|
| **Flow diversion** | | | | | | | | |
| MCA distal to bifurcation | 63 | 20 | 6 | SAC | Arterial rupture during FD retreatment of recurrence | Yes-6 | Haemorrhagic | Death |
| MCA distal to bifurcation | 22 | 8 | NA | Surgery | Aphasia with EEG abnormal activity in speech areas | No | Epilepsy | Prolonged hospitalization |
| **ASMO** | | | | | | | | |
| MCA bifurcation | 56 | 25 | 6 | PVO | Symptomatic stroke | No | Ischemic | Prolonged hospitalization |
| MCA bifurcation | 75 | 32 | 15 | SAC | Cardiac-related posterior circulation stroke. | No | Ischemic | New hospitalization |
| PCA aneurysm | 52 | 12 | 4 | SAC | Stroke related to in-stent thrombosis | Yes-3 | Ischemic | New hospitalization |
| AComm aneurysm | 68 | 2 | 2 | Surgery | Unrelated death (lung cancer) | Yes-6 | Death | Death |

FD: flow diversion; ASMO: alternative standard management options, mRS: modified Rankin Scale; LFU: lost to follow-up; MCA: middle cerebral artery; ACA: anterior cerebral artery; PCA: posterior cerebral artery, AComm: anterior communicating, SAE: serious adverse event; SAC: stent assisted coiling; PVO: parent vessel occlusion

**Online Table 7:** Primary efficacy outcomes in as-treated analysis.

| As-treated Analysis 1-year Outcome* | FD (n = 23) | ASMO (n = 23) |
|---|---|---|
| Treatment Failure (composite) (No) (%) | 6 (26.1) | 11 (50.0) |
| Clinical | | |
| mRS 6 | 1 (4.3) | 1 (4.3) |
| mRS 3-5 | 0 | 0 |
| SAH from aneurysm rupture | 0 | 0 |
| Retreatment | 1 (4.3) | 1 (4.3) |
| Immediate failure | 1 (4.3) | 2 (8.7) |
| Angiographic | | |
| Residual aneurysm (core lab) | 3 (13.0) | 7 (30.4) |
| Missing primary outcome | 0 | 1 (4.3) |

* RR = 0.52, 95%CI [0.23-1.17]; p=0.13