Flow Diversion in Aneurysms Trial: the Design of the FIAT study

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Summary

Intracranial aneurysms, particularly large and giant, fusiform or recurrent aneurysms are increasingly treated with flow diverters (FDs), a recently introduced and approved neurovascular device. While some rare cases may not be treated any other way, in most patients a more conventional, conservative, or validated approach such as coiling, parent vessel occlusion, or surgical clipping exists. Only a randomized clinical trial can answer the question of which treatment option leads to better patient outcomes.

We report the design of the FIAT study, a clinical care trial aiming to compare angiographic and clinical outcomes following treatment with a Flow-Diverter or with the best conventional treatment option.

The FIAT study will include both a randomized and a registry portion. Patients will be proposed randomization to either FD stenting or best conventional treatment option (observation, coiling, stenting, or clipping) as determined by the treating physician. FIAT will recruit a total of 338 patients, to show that i) FD stenting can be performed with an 'acceptable' immediate complication rate of less than 15% morbidity and mortality (defined as mRS > 2); ii) FD stenting can increase from 75 to 90% the proportion of patients with a "good outcome", defined as complete or near-complete occlusion of the aneurysm AND a good clinical outcome (mRS ≤ 2) at one year, as compared to the best conventional option.

The FIAT study provides a scientific and ethical context to care for patients eligible for flow-diversion therapy.

Introduction

Treatment of difficult aneurysms

Intracranial aneurysms (IAs), which have traditionally been treated with surgical clipping, are now increasingly treated with endovascular techniques, deploying mainly platinum coils into the cerebral vasculature in order to promote aneurysm thrombosis¹. The main drawback of this minimally invasive method is the incidence of aneurysm recurrences, (approximately 20%) following coiling, which may be even greater for aneurysms larger than 10 mm (up to 30-50%)²⁻⁴. For this reason, many large, giant, or wide-necked aneurysms thought unlikely to be durably occluded with endovascular coiling, are treated instead by deliberate parent vessel occlusion. Another conventional treatment that may be used is open surgery, with or without reconstruction of the parent vessel, or permanent occlusion of arteries with or without bypass. A third, recently introduced endovascular treatment alternative is to divert blood flow using a low permeability endoluminal stent known as a flow-diverter⁵⁻⁷. Flow diverting stents are made of a flexible tubular metallic mesh designed to normalize flow, close the aneurysm ostium and repair the parent vessel⁸⁻¹¹, by triggering thrombosis within the stent-covered aneurysm. Uncertainty regarding the best use of these new flow-diverting stents in terms of safety and efficacy has prompted the need for the trial proposed here.

Stenting

Experience with intracranial stenting started more than a decade ago with the use of balloon-expandable coronary stents in rare, proxi-

mal and easily accessible cases. The introduction of more navigable dedicated high porosity stents led to much more common use, estimated in the range of 10-30% of aneurysm patients in the US, although there is still little reliable data to justify their use. Originally approved to help retain detachable coils inside wide-necked aneurysms, stents are increasingly used as adjuncts to coiling¹²⁻¹³, but the additional risks due to implantation of a permanent potentially thrombogenic device remain poorly known¹²⁻¹³. Currently, more than 45 000 stents (Neuroform, Boston Scientific) have been implanted worldwide¹⁴, and this number continues to increase, driven primarily by fashion, market forces and hopes of improved long-term results of endovascular treatments.

The greatest clinical concern following deployment of these permanent intravascular foreign bodies are the thrombo-embolic risks to the parent vessel, as well as to branches covered or 'jailed' by the stent mesh. Most intracranial stents are thus designed to be porous, to occlude aneurysms in combination with coiling, while sparing the normal branches.

Flow diversion

As the prevalence of stenting has increased, the potential benefits of FD were recognized, and several attempts were made to treat aneurysms with stenting alone. Using high-porosity stents as mono-therapy (without coils) proved insufficient to promote aneurysm thrombosis in most cases¹⁵. However, subsequent attempts using overlapping, stent-in-stent techniques led to stable aneurysm occlusion in several small case series¹⁶⁻¹⁸. To capitalize on this property of stents, a new generation of flow diverters (FDs), with greater capacity to re-direct blood flow has been designed.

The use of stents in treating IAs is sometimes perceived as a paradigm shift: a move from occlusion of the aneurysm via coil packing of the sac, to repair of the parent vessel with a stent (addressing the site of weakness that led to aneurysmal dilation).

These devices have provided reconstructive eradication of lesions that could henceforth only be treated effectively with parent vessel occlusion, such as giant carotid or vertebral aneurysms producing mass effects. The use of FDs in treating aneurysms has already expanded to more common lesions such as recurring lesions after coiling, and many users contem-

plate flow diversion as the optimal treatment of standard or 'coilable' aneurysms, a question which will be the object of another recently launched trial, the Marco Polo trial (Sponsor: BALT International).

Clinical need for the use of flow diverters

The diversity of clinical situations (aneurysm or patient-related factors) that may be appropriate for a flow-diverting stent makes choosing the most appropriate trial design challenging. To capture pertinent clinical endpoints with a variety of realistic comparator treatments would normally entail designing multiple concurrent parallel trials, each with a too-large number of patients for a meaningful answer to be attainable. Yet there is an urgent need to compile good quality data on the success of the initial procedure, peri-procedural or delayed complications, and long-term anatomical results in all cases. In this situation, the temptation to resort to registries is strong, but observational studies and databases cannot protect patients from wishful thinking on the part of treating physicians, the pressure to use the latest most fashionable tool, not to mention the learning curves of therapists eager to acquire new skills¹⁹. Only a randomized clinical trial offers patients an opportunity to escape these unfortunate realities, with a 50% chance of random allocation to a more conventional type of treatment for their aneurysm. These alternatives, though better known than the more recent FD technology, also carry disadvantages and risks. Conservative management may be considered; it involves no immediate iatrogenic risk. However it does not offer protection against future rupture or progression of symptoms. Conventional open surgical options are also well known, but are, in most clinical situations that we are concerned with, at a higher risk of peri-operative complications, and with fewer chances of success than with the more common, normal size aneurysms. Coiling with or without high-porosity stenting is probably less risky, but in most situations targeted by this trial (large, fusiform, giant aneurysms and recurrences), risks are increased and chances of a permanent occlusion of the aneurysm much lower than with 'normal' aneurysms. Finally, parent vessel occlusion carries a significant risk of cerebral ischemia, despite precautions, such as testing with temporary balloon occlusion. Current indications for flow diversion may include:

- 1) Symptomatic large and giant cavernous carotid aneurysms.
- 2) Large or giant ophthalmic carotid and vertebral aneurysms.
- 3) Fusiform intradural aneurysms in other locations.
- 4) Recurrent or persistent lesions after failed endovascular treatment or surgery.
- 5) Patients that are judged difficult to treat using other endovascular or surgical techniques.

Complications associated with flow diverters

The greatest concern regarding FDs are the thrombo-embolic risks to the parent vessel, as well as to branches or perforators covered or 'jailed' by the stent mesh. A recent registry reports 4% morbidity and 8% mortality with the use of these new devices²⁰. These numbers will of course depend on the type of cases being recruited in the registries or trials, with a higher mortality and morbidity rate for complex and giant lesions²¹⁻²³. Another recently recognized complication is the occurrence of aneurysmal ruptures and intracranial hemorrhage following FD treatment of previously unruptured aneurysms (estimated to occur in 1-8% of FD treatments¹⁴). Although it remains difficult to draw conclusions from small series, these numbers are not substantially different from the risks typically associated with more conventional therapeutic options.

The proposed clinical care trial

The purpose of FIAT is to provide a prudent, controlled clinical context for the use of flow diversion, a promising but as-yet unproven treatment option, in the care of patients with difficult intracranial aneurysms. FIAT is a simple randomized trial designed to be integrated into daily clinical practice.

It addresses whether FDs truly offer a safe and more effective alternative to more conventional management options. Selection criteria are loose, in order to be of use to most patients and physicians currently confronting these difficult aneurysms. FIAT does not include any extra tests or clinical burden, using routine follow-up data collected on simple case-report forms. Endpoints are simple, clinical, meaningful, valuable and resistant to bias. FIAT is a multicentric, randomized, pragmatic, clinical care trial comparing anatomical and clinical results of endovascular treatment with FDs with the best

standard treatment (BST) as judged by participating clinicians. Patients with IAs for whom FD use is being considered will be recruited.

FIAT includes a pilot and a pivotal phase, as well as a registry for eligible but non-randomized FD patients. The BST comparator will be selected by the treating physician, who may choose from the most appropriate option among surgical clipping, parent vessel occlusion, coiling, high-porosity stenting with or without coiling, and conservative management, according to their best clinical judgement. FIAT requires approximately 344 patients with IAs judged to be treatable by FD to be enrolled and followed for one year. Patients that absolutely require treatment for their aneurysm and according to the clinical judgement of the physician cannot reasonably be offered any other management alternative (including conservative management) may also be recruited, but these will be analysed in a registry. Angiographic outcomes will be judged by a committee in an independent core laboratory.

Clinical outcomes (mRS) will be assessed by the treating physician. Safety of trial subjects will be periodically assessed by an independent Data Safety and Monitoring Committee. The trial will be conducted in at least ten centers, and completion will require five years (four years for recruitment and one year for follow-up).

Hypotheses

Primary hypothesis

Pilot and registry: For the pilot and registry portions of FIAT, the primary hypothesis is that the FD procedure can be performed with an 'acceptable' immediate complication rate, defined as less than 15 % mortality and morbidity, defined as an mRS > 2 at three months. Two hundred patients (200) could suffice to show that, if the observed number of patients with mRS > 2 is 10%, the 95% CI of the proportion is 7 to 14.9% (Newcomb method²⁴).

Pivotal phase: For the pivotal phase of FIAT, the primary hypothesis is that FD can increase the proportion of patients with therapeutic success, defined as complete or near complete occlusion of the aneurysm, AND an mRS ≤ 2 at three months post-treatment, from 75 to 90%. Demonstration of this 15% difference would require 112 patients in each group (total number of patients required would be 250 to account for losses).

Interventions

Treatment with flow diversion is to be evaluated against best standard treatment. The interventions are thus:

A/ endovascular treatment with flow diversion, including standard management of thrombo-embolic risk. Or

B/ Best standard therapy, which may be any of the following:

B1. Conservative management.

B2. Endovascular coiling with or without conventional stenting.

B3. Deliberate parent vessel occlusion with or without surgical bypass.

B4. Surgical clipping with or without bypass.

Registry: In this case, there will be no random allocation to treatment, because the only treatment alternative is FD (compassionate use).

The aim of treatment is the complete angiographic exclusion of the aneurysm, or, as complete an exclusion from the circulation as is possible, immediately or in a delayed fashion, while minimizing risks to the patient. This goal is considered the standard of practice. The anticipated thrombo-embolic risks from the use of FDs are such that patients will be prepared and covered with an effective dual anti-platelet medication for at least three months after FD implantation²⁵⁻²⁷. The lack of evidence in the neurovascular literature does not allow us to require a rigid protocol, and prescriptions will be according to local centres and expertise. The diagnosis and management of clopidogrel resistance will be according to normal care in each institution. There is no convincing evidence to require testing with commercially available aggregometers²⁶⁻²⁷.

*Selection criteria**Inclusion criteria*

Any patient with an aneurysm in whom FD is being considered for use by the treating clinician. Aneurysms may have recently ruptured, although it is anticipated that the risks associated with anti-platelet regimens in this context should make this option a rare choice by the treating physician.

Exclusion criteria

- Severe allergy, intolerance or bleeding disorder that prohibit the use of ASA or clopidogrel.
- Absolute contraindication to endovascular treatment or anesthesia.
- Patients unable to give informed consent.

Randomization

A minimization algorithm will be used to ensure balance between groups on the following parameters (hierarchical order): comparator intervention (i.e. type of BST selected) and centre.

Type, frequency and duration of follow-up

Clinical follow-up will be recorded at 24 hours, at discharge, at three to six months and at ten to 12 months. Clinical assessments will include evaluation according to the modified Rankin Scale at each follow-up. Follow-up CT-scan or MRI, will be performed at 24 h post-procedure or before discharge to detect silent peri-procedural events, if this is considered normal care at the institution where treatment was performed (Table 1).

Table 1 **Schedule of Evaluation**

Evaluation	Entry	Treatment	Discharge	2-6 months	10-12 months
Informed consent	X				
Documentation of disease/disorder	X				
Medical/treatment history	X				
Clinical assessment	X	X	X	X	X
Neurologic examination	X		X	X	X
Vascular imaging	X	X		X*	X*
Brain imaging			X*	X*	X*
mRS	X		X	X	X
X* Normal care or clinical indication					

Adverse events will be recorded immediately after the procedure and during the 12-month follow-up period.

Follow-up angiography will be at two to six months and at ten to 12 months. Catheter digital subtraction angiography (DSA) remains the gold standard to study residual lesions after coiling and stenting. In recent years, however, there has been a trend to rely on less sensitive but risk-free non-invasive imaging. Non-invasive imaging has become popular but the extent of metallic artefacts may not allow an appropriate assessment of results in some cases. Angiographic evaluation of treatment (invasive or non-invasive) will be performed according to normal care in each centre.

Outcome measures

End-point realization will be determined by the local investigators, with angiographic results sent to the FIAT Core Lab for independent review. Outcome measures, chosen to be hard clinically relevant end-points, are detailed below:

Pilot and registry: Mortality and morbidity will be determined by local investigators using the modified Rankin Scale (mRS) score. If mortality and morbidity (mRS >2) is less than 15% at the end of the pilot phase, FIAT will proceed to the pivotal phase and already registered and randomized subjects will be added to newly randomized subjects in the pivotal phase.

Pivotal phase: The incidence of therapeutic success will be measured, here defined as complete or near complete angiographic occlusion of the aneurysm, AND an mRS ≤ 2 .

Cross-overs: Patients in the control group that eventually require, according to the treating physician, treatment with FDs, will be counted as failures of conventional therapy, and the final angiogram before cross-over will be used as the primary outcome measure.

Recruitment rate and centers

The targeted lesions are not frequent lesions, thus we expect less than ten patients per year per center. We need to recruit at least ten centers that will recruit one patient per month for three years to reach the necessary sample size.

Centers will be experienced in endovascular treatment of aneurysms using both coiling (at least 100 patients will have been treated previously) and intracranial stenting (at least ten patients previously treated).

Duration of the trial

We plan a three-year recruitment phase, followed by a follow-up period of 12 months for all patients, with six months for data analysis, for a total time to completion of approximately five years.

Planned analyses

Descriptive statistics will be done on demographic variables and pre-operative and peri-operative data to compare the two groups at baseline. Means, standard deviations and range will be presented for quantitative variables and frequency tables for categorical variables. Comparability of the groups will be assessed through independent ANOVAs (quantitative data) or Mantel-Haentzel and chi-square tests (categorical data). The primary outcome will be compared between groups through a z-test for independent proportions at 12 months. Secondary outcomes and safety data will be compared between groups through independent t-tests (quantitative variables) or chi-square statistics (categorical data). The analyses of neurological data at follow-up will control for baseline data when possible (for tests done before discharge and at follow-up) using logistic regression, ANCOVA or Cox regression multivariate models. Finally, a logistic regression will be used to find variables capable of predicting success in both groups at 12 months. The method planned is a stepwise forward with $\alpha < 0.05$ to enter a predictor. Possible predictors include the type of the aneurysm (large aneurysms or recurrences), location, as well as other baseline characteristics.

Discussion

The introduction of flow-diverting stents to the endovascular armamentarium was initially greeted with enthusiasm, which has been tempered by increased reports of complications. The FIAT study has been designed to first: provide a prudent, scientific context for the safe clinical use of a new device and second: to answer the question of how this new tool compares to more conventional treatment options for patients presenting with difficult aneurysms.

FIAT addresses the problem of multiple comparators by grouping all the best standard therapies together into one arm of the study,

with the outcomes for individual therapeutic options captured as secondary endpoints. This grouping of comparator treatments is the only way that a randomized trial can be conducted to answer important questions for patients with these relatively uncommon aneurysms. The primary goal of the trial is to protect current patient being offered a treatment alternative that remains poorly known.

Physicians must continue to attempt to provide our patients with the best possible care in spite of uncertainty, and only randomized data can be relied upon in order to properly guide therapeutic decision-making.

FIAT offers a simple, pragmatic randomized trial, integrated into clinical practice. The simplicity of randomization and data collection will help assure that the trial can be performed without extra cost to participating centers. FIAT has been designed to provide a primary hypothesis that can be confirmed or refuted with

a number of patients that is feasible within the next few years.

Conclusion

Angiographic and clinical outcomes following treatment of large, giant, wide-necked or fusiform aneurysms with traditional options may be improved upon by the new generation of flow diverting stents.

However, only a randomized clinical trial can answer this question, and a large, simple trial, integrated into clinical practice, such as FIAT, can help physicians deliver the best possible care to patients harbouring these difficult aneurysms.

This study is registered at ClinicalTrials.gov [Identifier: NCT01349582].

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