REVIEW

The design of the STenting in Aneurysm Treatments (STAT) trial

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ABSTRACT

Unruptured intracranial aneurysms (UIA) are increasingly treated with endovascular treatment although this method continues to be associated with aneurysm recurrences in up to 30–40%, especially for large aneurysms or those with wide (>4 mm) necks. Although the significance of a recurrence remains unknown, they not only require angiographic follow-up but discovery sometimes leads to retreatment, with associated risks. Several strategies have been developed to decrease recurrence rates, including the addition of an endovascular stent to standard coiling. Stents may permit more complete coil occlusion, form a neointimal scaffold at the aneurysm neck and normalize blood flows. A randomized study of endovascular treatment of UIAs for aneurysms treated with or without stenting has not been performed. The design of the STenting in Aneurysm Treatments (STAT) trial is reported, which compares angiographic and clinical outcomes following endovascular treatment of UIAs with or without stents. The first phase of this pragmatic management trial will examine angiographic outcomes, in order to determine whether the addition of a stent to standard coiling can decrease recurrence rates, while the second phase of the study will determine if stenting is associated with increased patient morbidity and mortality. The STAT trial collaborators intend to enroll 600 patients, a size sufficient (at 80% power and 0.05 significance) to detect a decrease in recurrences from 33% to 20% by 1 year, and to verify that stenting does not result in an increase in the proportion of patients experiencing neurological disability (modified Rankin Scale score >2), from 6% to 12%.
Trial Registration No: ClinicalTrials.gov Identifier: NCT01340612.

BACKGROUND

Endovascular management is increasingly chosen as the initial treatment choice for unruptured aneurysms. Although good evidence exists for better 1 year patient outcomes for ruptured aneurysms,[1] there are no randomized data yet to support this practice for UIAs.[2] The greatest drawback to this minimally invasive alternative to surgery is the known higher incidence of aneurysm recurrences, estimated to reach 20–33% in some case series.[3 4] These troubling recurrences not only lead to a genuine concern for future hemorrhage (approximately 1% in some short term series), they may also sometimes require retreatment (5–10%), with the associated risks.[5–11]

In order to decrease the recurrence rate, a number of adjuncts to standard coiling have been introduced, including intracranial stenting. The deposition of these tubular mesh devices across the neck of the aneurysm offers several potential advantages: a stent can (1) prevent coil prolapse into the parent vessel bearing the aneurysm; (2) serve as a scaffold for neointima deposition across the aneurysm neck; and (3) perhaps play a role in the redirection of blood flow. Major concerns with a stent coiling strategy are the risks of (1) immediate or delayed stent related occlusion of branch or perforating vessels; (2) excessive neointima formation leading to parent vessel stenosis or occlusion; and (3) the obligatory addition of antiplatelet regimens required for stent use, with the associated risk of hemorrhagic complications.

The use of stenting to improve long term angiographic results is increasingly popular, particularly in the USA where in some centers stents are used in up to 20–30% of cases. Nonetheless, recurrences can still occur despite the use of stents.[4 12] Because stents are more readily used when recurrences are likely (with large or wide necked aneurysms), in the absence of a randomized trial, the efficacy of stenting in preventing aneurysm recurrences cannot be proven. Thus many years following the market availability of stents, we still lack reliable knowledge regarding the risk–benefit ratio of these devices.

We report the design of the STenting in Aneurysm Treatments (STAT) trial, the first multicenter randomized trial on the use of stents in the management of unruptured intracranial aneurysms (UIA), which will address the value of commercially available, currently approved, high porosity, self-expandable stents.

OVERVIEW OF STUDY DESIGN

The STAT trial is a randomized, multicenter, prospective, controlled trial comparing stent coiling to coiling alone. Adjudication of results will be performed by an independent core laboratory. All patients with a UIA eligible for endovascular treatment, with an aneurysm ≥10 mm, with a wide neck (≥4 mm) or with a major recurrence after previous coiling, would be proposed to participate in the STAT trial. The study will be conducted in 25–40 centers, aiming to enroll approximately 600 patients equally divided among the two arms, to obtain statistical significance in improving long term imaging results without doubling neurological deficits. The forecast duration of the study is 5 years. The STAT trial will be a pragmatic clinical care trial with loose inclusion criteria in order to apply to the majority of patients facing the dilemma. Endpoints are chosen to be

those clinically relevant outcomes normally measured by clinicians, with minimal intrusion into the delivery of standard care.

PRIMARY HYPOTHESIS OF STAT

The addition of an intracranial stent to an aneurysm coiling procedure will decrease the incidence of angiographic recurrence from 33% to 20% at 12 months.

SECONDARY HYPOTHESIS OF STAT

The use of intracranial stenting is *not* associated with a large increase in initial or long term neurological deficits (modified Rankin Scale score >2) from 6% to 12% at 12 months.

Calculation of number of patients

Retrospective studies of angiographic recurrence rates following endovascular treatment for these types of lesions are of the order of 29–33%.[3 4] For these difficult aneurysms, a decrease in the recurrence rate to 20% would be clinically significant. For the primary endpoint, a total sample size of 536 patients would allow the detection of such a difference with a power of 80% and an α error of 0.0125 (to account for subgroup analyses for the three main categories of lesion: large, wide necked and recurrent aneurysms). In addition, for the secondary endpoint, a total sample size of 524 would allow the detection of an increase in the proportion of patients with neurological deficits from 6% to 12%, with a power of 80% and an α error of 15%. In this context, the choice of a larger α is in accordance with a more prudent approach; it permits us to be confident that the addition of stenting has not doubled the complication rate. We thus estimate the sample size necessary for this trial to be 600 patients, with 1:1 allocation, in order to account for losses to follow-up, inadequate or incomplete imaging studies, and crossovers.

PRIMARY ENDPOINT

The primary endpoint is the incidence of angiographic recurrences at 12±3 months which, for the sake of this clinical trial, will be defined as: (1) a radiographic recurrence of the lesion; (2) an episode of intracranial bleeding; or (3) retreatment of the same lesion by endovascular or surgical means during the follow-up period. Although the clinical significance of angiographic recurrences remains to be determined, the primary outcome cannot be limited to an outcome as rare as a hemorrhagic event.

Angiographers at each participating center will ensure the best projection possible to demonstrate a possible residual neck at the time of follow-up evaluation. Two independent neuroradiologists blinded to the treatment groups will determine the presence of angiographic recurrence (core laboratory). Any progression of a residual lesion will be considered a recurrence. Recurrences will be further divided into major or minor, with a major recurrences considered to be any saccular lesion which ideally would be retreated. Angiographic results will be scored according to a previously published classification system[13] and groups will be compared initially and at follow-up.

The recurrence rate will be calculated as the number of recurrences divided by the number of aneurysms in each group for both intent to treat and per protocol populations.

SECONDARY ENDPOINTS

The secondary endpoints will include: (1) initial angiographic occlusion success rate; (2) morbidity rate; (3) mortality rate; (4) number and severity of adverse events; and (5) incidence of in-stent stenosis. A morbid event will here be considered an adverse event of any severity being possibly or probably related to the disease or the treatment which occurs during the 12 month follow-up period. In-stent stenosis will be considered to have occurred when the luminal diameter is reduced by ≥50%, as determined by the core laboratory.

PLANNED TRIAL INTERVENTIONS AND TECHNICAL FREEDOM

Endovascular aneurysm coiling with or without stenting will be performed once for each patient. Treatment will be performed within 6 weeks of randomization, according to standards of practice and under general anesthesia. Patients allocated to coiling alone will be premedicated with aspirin (ASA) only. Patients allocated to stent coiling will be premedicated with clopidogrel 75 mg/day for 5 days and ASA 325 mg/day for 1 day before the procedure. The ASA–clopidogrel combination will be continued for at least 3 months after the procedure. Details regarding endovascular technique, type of coils, use of adjunctive techniques such as balloon remodeling, whether the stent is placed prior to or following coiling, as well as post-treatment medical management issues, will be left up to the treating physicians. To ensure the safety of the procedure, patients randomized to the coiling alone group may be treated with a stent as a bail-out maneuvers if judged appropriate by the treating physician. Similarly, if the patient is allocated to stent coiling, and the addition of a stent is judged inappropriate or dangerous at the time of the procedure, the treating physician may choose to not use the stent. These unusual cases will be the object of specific analyses.

METHOD OF ALLOCATION

Patients will be randomly allocated into one of two treatments groups: (a) coiling alone or (b) coiling plus stenting, using a centralized minimization procedure to ensure balance between groups, taking the following aneurysm factors into account: (decreasing hierarchical order) (1) aneurysm size ≥10 mm and (2) recurrent aneurysm post-coiling.

Inclusion/exclusion criteria

Selection criteria are described in box 1.

JUSTIFICATION OF INCLUSION AND EXCLUSION AND MINIMIZATION CRITERIA

Uncertainty and equipoise

To be eligible for participation in this trial, the patient must be eligible for both treatment options. Because STAT is a pragmatic trial, we have not attempted to formalize which aneurysms would clearly be better treated with one type of treatment over the other. In the absence of convincing evidence, such criteria would be at best arbitrary and at worst erroneous.

Aneurysm related factors

Size

The risk of a major recurrence following coiling of an intracranial aneurysm greater than 10 mm has been reported to be as high as 34% compared with <10% when aneurysms are smaller.[3]

Neck size

The risk of a major recurrence following coiling of an intracranial aneurysms with a wide neck (≥4 mm) has been reported to be 35% compared with 13% when the neck is narrow.[3]

Recurrent aneurysms

These lesions have proven themselves to be resistant at least once to simple coiling, and they may constitute a group of more

Box 1 Selection criteria for the study

Inclusion criteria
- Patient at least 18 years of age with at least 2 years of remaining life expectancy
- At least one documented, never ruptured, intradural, saccular intracranial aneurysm
- Index aneurysm is large (≥10 mm), and/or has a wide neck (≥4 mm) or has previously recurred following endovascular coiling
- The anatomy of the aneurysm is such that endovascular treatment is possible with or without stenting
- The treating interventionalist is content to use either technique
- The patient has given fully informed consent

Exclusion criteria
- Patients with other aneurysms requiring treatment during the same session
- Patients with arteriovenous malformation associated aneurysms
- Patients with recent aneurysm rupture (within the previous 3 months)
- When parent vessel occlusion is the primary intent of the endovascular procedure
- Patients with baseline modified Rankin Scale score >2
- Pregnant patients (randomization (and treatment) may be delayed until after delivery)
- Patients with absolute contraindications to anesthesia, endovascular treatment or severe allergies to antiplatelet drugs or contrast agents

difficult aneurysms than other large or wide necked aneurysms. Patients treated electively for a first recurrence after initial coiling have a re-recurrence rate of up to 50%.[3]

Patient follow-up

Patients from both trial arms will be seen in clinic at approximately 6 weeks as part of routine follow-up care. Patients will be followed with an angiographic study (invasive or non-invasive, depending on local practice patterns) at 1 year, along with a routine clinic visit. At the time of follow-up, a modified Rankin Scale score will be determined and inquires made regarding possible aneurysm rupture, other admissions or retreatment.

Planned analyses

Descriptive statistics will be done on demographic variables, preoperative and postoperative factors to compare the two groups at baseline. Means (SDs) and ranges will be presented for quantitative variables such as size of aneurysms and frequency tables for categorical variables (such as the number of patients with multiple aneurysms). Those statistics will be broken down by center and by treatment arm. Comparison of the groups will be assessed through independent ANOVA (quantitative data) or Mantel–Haentzel and χ^2 tests (categorical data). The main statistical test will involve comparisons between the recurrence rates (for both intent to treat and as treated populations) using a z test for independent proportions at 12 months.

Secondary outcomes and safety data will be compared between groups using independent t tests for quantitative variables and χ^2 tests for categorical variables. The analyses of neurological data at follow-up will control for baseline data using logistic regression, ANCOVA or Cox regression multivariate methods. Finally, a logistic regression analysis will be performed to find variables capable of predicting recurrence in both groups at 12 months. The method planned is a stepwise forward with an α value of <0.05 to enter a predictor. All tests will be interpreted with a 0.05 level of confidence.

Frequency of analyses

To prevent the α spending that follows every additional analysis, the data will only be analyzed once, after the 1 year follow-up imaging study has been completed in all participants. Safety data (occurrence of severe adverse events, treatment related complications and hemorrhages) will be reviewed periodically by the Data Safety and Monitoring Committee that will meet at least on a yearly basis. The primary outcome will be assessed at 1 year.

DISCUSSION

The most fundamental clinical dilemma, whether UIAs should be treated or not, will not be addressed by the STAT trial. A previous randomized controlled trial designed to compare coiling and conservative management, the Trial on Endovascular Aneurysm Management (TEAM)[14] was interrupted due to insufficient recruitment. The choice of whether surgical clipping or endovascular coiling is the best initial choice of modality for UIAs is currently the subject of another ongoing randomized trial (Canadian UnRuptured Endovascular versus Surgery (CURES) trial).[2] STAT addresses the problem of when patients present with aneurysms considered being difficult to treat with endovascular methods, does the addition of a stent decrease recurrence rates? And, if so, is stent use associated with an increased amount of patient morbidity?

Large scale international randomized controlled trials are difficult to organize and implement. The financial, regulatory, legal, contractual and organizational hurdles are so numerous that launching such an effort requires years of hard work, during which time financial support is difficult to secure. Nevertheless, we must attempt to provide our patients with the best possible care in spite of the uncertainty. We have repeatedly demonstrated the failure of the previous ways of doing things. It is now time to get our act together, and to provide care under the protection of scientific methods.[15] As clinicians, our patients should either receive care that is guided by evidence or be treated with as yet unproven therapies under the protection of a well designed randomized clinical trial.

What we need are large, simple, pragmatic randomized trials that are integrated into clinical practice. Follow-up visits and tests are the same as those performed as a part of routine care. Endpoints must be predefined, simple, meaningful and resistant to bias. Data can be collected on simple electronic forms. The simplicity of the procedure and lack of extra requirements will help assure that the trial can be performed without extra cost to participating centers. STAT represents the latest contribution to this generation of clinical care trials.

CONCLUSION

Intracranial stent use to promote stable aneurysm occlusion following endovascular coiling is becoming increasingly popular, in the absence of randomized data. It is possible that the addition of a stent to an aneurysm coiling may increase patient morbidity and mortality. By comparing angiographic and clinical outcomes in randomized patients with large, wide necked or recurrent aneurysms, it will one day be possible for the endovascular community to know whether stenting of these difficult aneurysms is of benefit to patients.

Correction notice This article has been corrected since it was published Online First. The section head has been amended to Hemorrhagic stroke.

Competing interests None.

Ethics approval Ethic approval was obtained from the CHUM Institutional Ethics Committee.

Contributors JR and TED designed the study. They are also the PIs of the study.

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