# A Randomized Trial on the Safety and Efficacy of Endovascular Treatment of Unruptured Intracranial Aneurysms Is Feasible

J. RAYMOND, M. CHAGNON *, J-P COLLET **, F. GUILBERT, A. WEILL, D. ROY

*CHUM Notre-Dame Hospital, Radiology department,*
*\* Department of Mathematics and Statistics, Université de Montréal,*
*\*\* Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec; Canada*

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## Summary

*The safety and efficacy of endovascular treatment of unruptured intracranial aneurysms remain undetermined. A randomized trial may be the best way to demonstrate the potential benefits of endovascular management.*

*We propose a randomized, prospective, controlled trial comparing the incidence of subarachnoid haemorrage of patients treated by endovascular coiling as compared to conservative management. We would also study a composite outcome combining SAH and the morbidity of treatment. All patients with one or more unruptured aneurysm >> 3 mm eligible for endovascular treatment would be proposed to participate. The study would be conducted in 40-50 centres. The entire study would enrol 1800 patients, recruited over three years and followed for five years, but would be preceded by a feasibility study on 200 patients.*

*A randomized trial comparing endovascular and conservative treatment could have an important impact on the clinical management of intracranial aneurysms*

## Introduction

The care of patients with unruptured aneurysms has been described as the most vexing scientific question confronting neurosurgeons, neurologists and interventional neuroradiologists [1,2]. The prevalence of intracranial aneurysms is still unknown, but has been estimated at 1 to 5% of the adult population [3]. With the increasing availability of non-invasive imaging of the brain, more and more unruptured aneurysms are being discovered during the investigation of unrelated symptoms. Most aneurysms remain asymptomatic until the day they rupture, an event that occurs with an annual incidence of 8-10/100 000 [4-6]. Subarachnoid haemorrhage is associated with a high morbidity and mortality (45-75%) [7-9] despite the advances of modern surgical and medical management [8,10]. Thus a preventive treatment strategy is appealing [2,3,10-15]. The annual risk of bleeding from an unruptured aneurysm is controversial, but most series and meta-analysis have reported a small annual risk, between 0.5-2% [15-22].

Any preventive treatment should consequently be very safe. A controversial study in 1998 suggested the natural history was more benign than previously thought, while the risks associated with surgical clipping may have been underestimated [23].

Surgical treatment of intracranial aneurysms is increasingly being replaced by the less invasive endovascular alternative [24-33]. Endovascular coiling is effective in preventing rebleeding of ruptured aneurysms [26,31]. An international randomized trial has shown that endovascular treatment is safer and does improve the out-

come of patients treated after subarachnoid haemorrhage compared to surgical clipping[31].

Coiling has also been considered a valuable alternative treatment for unruptured aneurysms[32,33]. Endovascular treatment may offer a less morbid management of unruptured aneurysms that could prevent the morbidity associated with SAH[32-35]. One drawback of endovascular treatment is the risk of angiographic recurrences, found in 10-20% of patients, but the clinical consequences remain modest: haemorrhages after treatment of ruptured or unruptured lesions have been reported in 0.1 to 1% of patients[31-33,36,37]. Recurrences are significantly less frequent after endovascular treatment of unruptured as compared to ruptured aneurysms[36,37].

The clinical efficacy and benefits of endovascular treatment of unruptured aneurysms have yet to be demonstrated however.

## Current Evidence and Controversies Regarding Haemorrhagic Risks and Treatment of Unruptured Aneurysms

A detailed comprehensive review of publications on unruptured aneurysms can be found in[1].

A nonrandomized prospective registry comparing patients selected for conservative management with patients selected for surgical or endovascular treatment is currently the most significant study on unruptured intracranial aneurysms (ISUIA)[38].

This laudable effort suffers from multiple systematic biases, a consequence of the current "best clinical judgment" attitude. We and others suspect that patients recruited in this study are selected in such a fashion that those felt to be at high surgical risk and at high risk for rupture are offered endovascular treatment; patients with low surgical risks, at high risk for rupture are treated by surgical clipping; those with lower rupture risk are being declined for both invasive treatments[10,38,39].

This effort does however provide some numbers for surgical and endovascular risks, although they may be overestimates[38]. Although the scientific validity of this approach regarding the natural history of unruptured aneurysms is weak, the resulting estimates of the annual risks of rupture are now probably enjoying the widest level of acceptance within the neurological communities. The overall rupture risk for conservatively managed lesions was

3% over a mean follow-up of four years, still an underestimate, in our opinion, because of a systematic selection bias.

The previously reported results of the retrospective study from the same group had stirred much discomfort and a high level of scepticism but were widely publicized[2,18,39-45]. Included in this retrospective cohort were patients that survived for long periods without symptoms or rupture, but by design, were excluded patients that had lesions at high risk of haemorrhage. This publication had the merit of raising concerns regarding iatrogenia in the neurosurgical and neuroendovascular communities, generally in favour of preventive interventions.

Neurosurgical publications on unruptured aneurysms are usually nonrandomized historical cohort comparisons between current patients who receive therapy and former patients who received no therapy[1,5,46]. Although patients with multiple aneurysms that survived the rupture of a previously treated aneurysm are over-represented, these surgical series reflect more closely the population of patients that come to medical attention in neurosurgical or endovascular services. The annual risk of rupture reported in these series is higher, in the range of 2%, as summarized in the meta-analysis by Rinkel[5].

A Stroke Council[47] has stated, regarding unruptured aneurysms, that "nonrandomized historical cohort comparisons between current patients who receive therapy and former patients who received no therapy, series without control groups, or non-randomized studies are the only evidence available", supporting recommendations at a Grade C level only. This type of recommendation suggests an array of potential clinical actions, all of which might be appropriate. Thus there are currently no practice guidelines for the management of unruptured aneurysms.

## Unruptured Aneurysms: Patterns of Practice

It would be essential to pre-emptively treat patients deemed to be at high risk for rupture to prevent the morbidity and mortality associated with SAH. It is also crucial to avoid iatrogenic injuries to patients "destined to coexist peacefully with their unruptured lesion"[1].

Continuous efforts at identifying subgroups of patients with higher risks of rupture to target a population in which treatment may be indi-

cated has unfortunately been confronted by the fact that a high-risk natural history is often associated with a high surgical risk [38,48].

Clinicians attempt to tailor their decisions to individual patients. Many neurosurgeons believe they can identify patients in whom it is reasonable to offer treatment to eradicate the threat of a future rupture, especially in young and middle-aged adults, even though benefits cannot be scientifically proven [2,10,16,40,41].

Other groups, often led by neurologists, believe that more than a lifetime of rupture risk is taken by operating on patients with unruptured lesions [23,38,43,47].

In the meantime clinicians have to manage patients with unruptured aneurysms, relying on "clinical judgment", using various homemade algorithms, taking into account age, size and location of aneurysms, previous medical and familial history, the patient's attitude toward knowing they have an untreated aneurysm, as well as an "honest" assessment of neurosurgical skills, limitations and complications 1. Unfortunately this decision-making process is heavily influenced by the clinician's culture and personality, with surgeons often favoring invasive and neurologists conservative management. The uncertainty regarding the management of unruptured aneurysms has not progressed in the last 20 years.

The neurosurgical literature acknowledges the "enormous appeal of a randomized trial from a theoretical perspective", but believes it is impossible "from a pragmatic perspective" [39].

Endovascular treatment with detachable coils may provide a new angle to this debate.

### Potential Benefits of Endovascular Treatment of Unruptured Aneurysms

Epidemiological comparisons suggest that endovascular treatment of unruptured aneurysms is safer than surgical clipping [34,35,49-52]. A state-wide database in California showed that surgical treatment of unruptured aneurysms was twice as likely to lead to mortality, and 1.7x to morbidity, defined as transfer to a rehabilitation centre, as compared to endovascular treatment [52]. This work also emphasized the steady decline of the endovascular morbidity over the years, while the surgical morbidity remained stable, as well as the relationship between low-volume activities and morbidity. The authors suggested unruptured aneurysms should be tre-

ated in high-volume centres. In University hospitals, the in-hospital mortality was six times more likely with surgical clipping of unruptured lesions compared to coiling [35].

ISAT has shown that for ruptured lesions that are eligible to both surgical and endovascular treatment, the endovascular approach decreases the absolute morbidity by 7% at one year. These results cannot be extrapolated to unruptured lesions. Because ruptured lesions have a high tendency to rebleed, ISAT is however reassuring regarding the short-term efficacy coiling, criticized for more frequent incomplete initial occlusions and delayed recurrences as compared to surgical clipping [53]. The efficacy of endovascular coiling of unruptured aneurysms in the prevention of haemorrhagic events remains to be determined. Long-term follow-up of patients (with both ruptured and unruptured aneurysms) treated by coiling have shown that delayed ruptures remain rare, in the order of 0,15-0,3% per year [37,54]. Case series from single centres suggest that treatment is effective but cannot prove this pretension because of the small number of patients and relatively short follow-up periods [32,33,55-57]. A Stroke Council has stated that it was premature to judge the efficacy of endovascular treatment of unruptured aneurysms [47].

It is time to determine the efficacy of endovascular management in a scientifically valid trial.

### A Trial Comparing Endovascular and Surgical Management Is Not Possible

The Stroke council suggested a randomized trial comparing coiling and clipping, but this was judged by others impossible to realize [18,39,43,58].

Because the natural history of unruptured aneurysm is still controversial, and treatment risks may still be too high, both options may not be beneficial to most patients 23, 38. The "ideal trial" would propose randomization to conservative, surgical and endovascular groups. The neurosurgical community at large has manifested its opposition regarding a randomized trial through editorials [18,39,40,42].

To include three randomized groups in a trial would be difficult. Lesions and patients best treated by the endovascular route (posterior circulation aneurysms or older patients) [38,43,48] may be complementary to lesions best treated by surgical clipping (anterior circulation lesions

in young patients) while both options may give inferior results in patients at highest risk of rupture (such as large and giant lesions of the basilar bifurcation for example [38]). Besides randomization to three groups, subsets of patients and aneurysms may need to be studied [39]. Sample sizes may become prohibitive.

Another possibility would be to compare conservative and "active treatment", surgical or endovascular, but such a design would necessitate rigid criteria for the selection of the treatment options. These criteria may be the object of endless debates and could no longer be pertinent by the end of a long trial.

We propose that the efficacy of endovascular treatment of unruptured aneurysms regarding prevention of haemorrhage should first be compared to conservative management.

## The Need for Scientific Validation

Randomized clinical trials are the most effective means of determining objectively the relative efficacy and "toxicity" of new medical interventions [59]. They are feasible and have shown their value in the evaluation of surgical techniques commonly performed without prior demonstration of their clinical benefit. The impact of some of these trials on the everyday management of patients has been of major importance [60,61].

Endovascular treatment of aneurysms first concerned patients with lesions at high risk for surgical clipping [25,27,62]. The technique became popular in the management of common lesions, including unruptured aneurysms, without an objective assessment of risks versus benefits. Although many are convinced of the efficacy of treatment, coiling of unruptured aneurysms remains controversial. To clinicians who believe neurointervention is more an art than a science, and that treatment has to be tailored to each patient and according to one's skills, we suggest that the scientific information obtained through a randomized trial is most likely to help the practice of their art, or to improve the accuracy of their clinical judgment.

If a previous council has stated it was premature to judge the efficacy of endovascular treatment, time alone, retrospective or even prospective observational cohort studies cannot provide an unequivoqual answer to the fundamental questions of efficacy and benefits of treatment of unruptured lesions.

A most pertinent aspect of the problem is how much risk can we afford to take immediately to prevent a future haemorrhagic event? The answer of course depends on the natural history of unruptured aneurysms, and more particularly on the haemorrhagic risks of patients that could be eligible for endovascular treatment.

Once the haemorrhagic risks associated with this target population is identified, we also need to verify that risks of the procedure, and specifically risks in that target population, are substantially less than the risks of the disease.

Although we acknowledge that it may be difficult to prove the overall benefit of endovascular as compared to conservative management of unruptured aneurysms, the most pertinent aspect of the question, we propose that only a randomized trial can offer valid answers to questions regarding haemorrhagic risks of conservative management as well as treatment-related morbidity, as they may apply to the population encountered in endovascular services.

Because endovascular treatment is being performed in thousands of patients each month worldwide, it is becoming urgent to find answers to these questions.

To enrol a patient in such a trial necessitates the acknowledgment that we do not know for sure what is the best management of his condition. In patients in whom risks of treatment may appear reasonable, the risks of future haemorrhage may also be modest. Another lesion presenting characteristics that are of concern for haemorrhages, may also carry increased immediate procedural risks [38].

## Aneurysm Size and Other Risk Factors

Most investigators would agree that the risk of rupture increases with lesion size (reviewed by Weir [1]). The controversy mainly regards a magical number under which the lesion would be safe to observe. This controversy came to a zenith after publication of the retrospective group of the ISUIA [2,18,23,39-45].

This article reported an extraordinarily low risk of haemorrhage for unruptured lesions smaller than 10 mm in patients without a prior history of haemorrhage from another lesion (0.05%/ year). This study was severely criticised, on methodological ground, for a systematic selection bias for lesions at lesser risk of bleeding [19]. Patients with unruptured aneurysms

associated with a prior history of a treated ruptured aneurysm had a yearly risk of 0.5% for the same size of lesions. In fact for this group of patients, the rate of rupture was independent of aneurysm size. Furthermore, many neurosurgeons pointed out that the mean size of ruptured aneurysms is between 7 and 8 mm [1].

A prospective non-randomized observational study published by the same authors has now lowered the critical size to 7 mm. They no longer demonstrated a significant difference for patients with a history of rupture of another aneurysm. Patients with aneurysms 7 mm or larger are now said to have a risk of bleeding of 2.6 to 14.5% over a five year period, depending on location (IUSIA) [38]. We believe these numbers that have been revised are still too low because of the selection bias intrinsic to the design of the study.

Aneurysms >> 10 mm usually represent less than 15% of all unruptured lesions [16,19,32,33].

In the size range 4 to 10 mm ruptured aneurysms are seen twice as frequently as unruptured lesions [19]. More than 90% of ruptured aneurysms treated during ISAT trial were less than 10 mm. In our own series of unruptured aneurysms treated by coiling, 68% of lesions were < 10 mm [33]. Aneurysms >> 10 mm have a significant higher risk of recurrence after endovascular treatment [37]. Thus a preventive strategy limited to these lesions would apply to only a small number of patients, those more likely to have unstable results.

Many clinicians would not operate on a single unruptured 3 mm aneurysm, and this size was a lower limit in the ISAT study, to minimize haemorrhagic complications during treatment [26,54,63,64]. We propose to exclude aneurysms < 3 mm, as well as giant aneurysms (≥ 25 mm), a small group of patients for whom coiling is poorly effective [37].

Other risk factors for haemorrhage have been identified such as aneurysm location (basilar aneurysms, posterior circulation aneurysms, posterior communicating artery aneurysms are at higher risk, cavernous aneurysms have a much lower risk), midline location, the presence of sacculation and the history of a previously treated ruptured lesion, smoking and hypertension [1]. To take into account all factors to construct subgroups and design the trial accordingly becomes impossible. However, we acknowledge the need to exclude cavernous lesions that are not located in the subarachnoid space. A trial would record characteristics of patients and aneurysms to ensure comparability of treated and control groups and search for more data on the natural history of the disease and on the risks of the procedure. Clinical monitors in each centre would also record patients with unruptured aneurysms not recruited into the trial, their characteristics, and how they were managed.

## Risks of Endovascular Treatment and Future Advances

Most endovascular series are single centre observational studies [32,33,55-57,65,66]. The risks of treatment have varied from 1 to 6%, with a good outcome in close to 99% of patients. Mortality in these single centre experiences has been minimal or less than 1%. There are some indications that risks increase with lesion size, posterior circulation aneurysms, and width of the neck [38,67,68]. Non-randomized clinical series tend to underestimate risks because of a publication bias for best results.

There are also less favourable results collected from a prospective observational multicentric study [38]. It is of importance to note that the mean size of treated lesions was 13 mm, significantly larger than the mean size of lesions treated by surgery or conservative management in the same publication [38]. One third of patients presented with mass effect or cranial nerve palsies, a clear indication of systematic bias. The mean aneurysmal size of this cohort also differs from most endovascular series, and size is an important risk factor that may explain the relatively high morbidity (7%).

The morbidity that would be associated with endovascular management of unruptured aneurysms in a multicentric trial still needs to be defined.

There may be technical developments during the time period necessary for the realization of this trial. The current platinum coils are very safe. It is unlikely that more effective coils or devices will prove to be safer, even in the distant future, because such a demonstration would necessitate an impossibly large-scale study, in the range of multiple thousands of patients. Conversely, new devices may improve angiographic results, but clinical consequences of angiographic recurrences are modest [37,54].

Thus, proving a significant decrease of an already very low haemorrhagic risk (as opposed to lesser angiographic recurrences) would necessitate sample sizes that are beyond feasibility. The benefits of endovascular treatment regarding haemorrhagic risks, if shown with current platinum coils, are likely to remain true with future coil modifications, provided they have shown at least equivalent safety.

It is time to determine if endovascular management is effective in the prevention of subarachnoid haemorrhage, and if it is, whether it is beneficial to most eligible patients.

## The Proposed Trial

We propose a randomized, multi-centre, prospective, controlled trial comparing the incidence of subarachnoid haemorrhage of patients with unruptured aneurysms treated by endovascular coiling as compared to conservative management. We would also propose a composite outcome combining the incidence of SAH and the morbidity of treatment. Secondary endpoints would include clinical outcome at five years. All patients with one or more unruptured aneurysm > 3 mm eligible for endovascular treatment would be proposed to participate. The study would be conducted in 40-50 centres. The entire study would enrol 1500-1800 patients equally divided between the two groups. The duration forecast of the study is eight years, the first three years being for patient recruitment plus a minimum of five years of follow-up.

## Primary Outcome

The primary outcome, the rate of subarachnoid haemorrhage, will be defined as the number of haemorrhagic events divided by the number of patients in each group for both intent-to-treat and per-protocol populations. Haemorrhages will be recorded as clinical symptoms appear at anytime, as they are discovered, at the yearly follow-up assessments or at five years, or at time of death. This endpoint should determine the efficacy of endovascular treatment in the prevention of haemorrhagic events.

To take into account treatment-related risks, a composite endpoint would include morbidity of treatment and follow-up haemorrhagic events. Morbidity would be defined as any treatment or disease-related complication that

would lead to dependency at one month and one year (Modified Rankin 3 and more). This analysis would assess benefits of endovascular treatment as compared to conservative management.

Secondary outcomes would include overall morbidity and mortality at one and five years.

## Outcome Measures

Clinical assessments will include evaluation according to the Modified Rankin Scale at one month, at yearly intervals and at five years using a standardized questionnaire. At the end of the follow-up period, both groups will be evaluated using the Rankin scale and the mini-mental state examination or the telephone interview for cognitive status. Non-invasive angiography may be performed in both groups at five years to learn more about the morphological evolution of unruptured aneurysms.

Catheter angiography would be informative at five years in patients treated by endosaccular coiling, in an effort to better define the incidence of long-term angiographic recurrences. In the case of a positive trial regarding the haemorrhagic risks, but equivocal benefits in terms of morbidity, this data may offer an indication regarding long-term benefits of endovascular management, if there is any.

## Sample Size

There are practical considerations that limit the size of the population that can be studied. ISAT, the largest randomized study ever performed in the neuroendovascular field, included over 2000 patients that were followed for one year [54]. Recruitment of a larger population that would need to be followed for a significant number of years could appear unrealistic. We believe the sample size needs to be restricted to approximately 1800. If 50 centers participate in the study, one patient a month per centre (less than the ISUIA) is sufficient to reach recruitment of 1800 patients in three years.

## Duration of Follow-up

Efficacy in the prevention of an event that cannot be predicted and which occurs with an incidence between 0.5 and 2% per year necessarily implies a relatively long follow-up. The follow-up period still has to remain within rea-

sonable limits in order not to jeopardize the feasibility of the trial. We believe a minimum observation period of five years is acceptable, provided that recruitment can be done in a compact fashion (within three years).

## Hypotheses

The sample size of the proposed trial is based on the following estimates:

1) The incidence of haemorrhagic events in the conservatively managed group will be 7% at five years (range 3-10%). For haemorrhagic risks below 3%, the size of the population necessary to show efficacy would be prohibitive.

2) Endovascular treatment will lead to a decrease in the incidence of haemorrhagic events to 1% or less (range 0.1-1%). Such a decrease would be a significant clinical advance.

3) Treatment morbidity, defined as a poor outcome at one or five years (modified Rankin 3 and above), will be 3% (range 1-6%).

Table 1 **Examples of total sample sizes for given differences**

| Incidence of SAH | Observable incidence | | Total population (n =) |
|---|---|---|---|
| | Conser-vative | Endova-scular | |
| | 3% | 1% | 1402 |
| | 5% | 3% | 2570 |
| | 5% | 2% | 1054 |
| | 5% | 1% | 542 |
| Composite outcome[1] | Conser-vative | Endova-scular | Total population (n =) |
| | 7% | 4% | 1558 |
| | 7% | 5% | 3682 |
| | 10% | 5% | 762 |
| | 10% | 6% | 1232 |
| | 10% | 7% | 2266 |

[1] *SAH and treatment related morbidity (Modified Rankin 3 or more)*

Table 2 **Inclusion and exclusion criteria**

| Inclusion Criteria | a. At least one documented subarachnoid aneurysm, unruptured, not previously treated |
|---|---|
| | b. At least one aneurysm is suitable for endovascular treatment |
| | c. Lesion size < 3 mm |
| | d. Patient aged 18 or older |
| | e. Patient is independent (Modified Rankin 1 or 2) |
| | f. Life expectancy more than five years |
| | g. Patient has signed the consent form |
| Exclusion Criteria | a. Patients with intracranial haemorrhage |
| | b. Lesion (s) unsuitable for endovascular treatment |
| | c. Patient with cavernous aneurysms (unless another unruptured subarachnoid aneurysm is present) |
| | d. Aneurysms « 3 mm |
| | e. Giant aneurysms (» 25 mm) |
| | f. Patients with a poor outcome (Rankin scale » 3) after the rupture, surgical or endovascular treatment of another aneurysm |
| | g. Patients with associated arteriovenous malformations |
| | h. Patients with new severe progressive symptoms in relationship with the aneurysm (headaches suggestive of impending rupture, third-nerve palsy, mass-effect from non-cavernous lesions). |
| | i. Patients with previous intracranial haemorrhage from unknown causes |
| | j. Patients in whom surgical clipping of unruptured aneurysm is planned |
| | k. Patients with contraindications to anaesthesia or endovascular treatment such as severe allergy to contrast media |
| | l. Pregnancy |

4) A composite measure of haemorrhagic events plus treatment morbidity in the treated group would be 4% (range 1-6%). Presuming a high rate (10% over five years) of SAH in the conservative group, the highest morbidity that could still demonstrate a benefit for endovascular treatment with a realistic sample size is 6%.

Examples of differences that could be demonstrated as statistically significant with such sample sizes are given in table 1. Thus if the incidence of SAH in the control group is as low as 3% over five years, demonstration of efficacy of endovascular treatment may be feasible, but an overall benefit would be impossible to show. Conversely if the incidence of SAH is as high as 10% over five years, it becomes possible to show an overall benefit of treatment if its morbidity remains below 6%.

### Inclusion/ Exclusion Criteria

We suggest keeping exclusion criteria at a minimum in order to minimize effects on future generalization of results. Patients with multiple lesions can be included and there is no need to treat all lesions. Patients with a good outcome following endovascular or surgical treatment of another lesion can also be proposed to participate. Proposed criteria are summarized in table 2.

### Costs of Endovascular Management

We could conduct a cost, cost-effectiveness and cost-utility analyses to estimate the cost of the resource usage associated with endovascular treatment of unruptured aneurysms in selected centres. The analyses would focus on the global direct costs of interventions. The total costs of intervention, hospitalisation, intensive care unit, supply including the coils, procedural costs, pre and postoperative imaging studies, secondary interventions and medications would be assessed. Downstream costs will be collected during the years of follow-up. The costs of these visits and tests as well as the expenses for the medications involved will be calculated. The costs of additional expenses resulting from complications should also be assessed. In cost-effectiveness analysis the total cost of endovascular patients would be calculated per clinically successful intervention.

### Feasibility Study

The trial would begin with a feasibility phase designed to verify the credibility of the hypotheses and the feasibility of the study.

After one year, approximately 200 patients would be recruited in 15-20 centres, and we expect that morbidity related to treatment would affect 0-9 patients.

Based on the confidence intervals of our hypotheses, haemorragic events during first year of follow-up in the treated and control groups should not exceed three and five respectively.

### How Would the Results of the Trial Be Used?

A randomized trial would offer the best evaluation of the efficacy of endovascular coiling of unruptured aneurysms. Additional data would be obtained on the natural history of the disease as well as risks involved with endovascular treatment. Most importantly, if risks of endovascular management are estimated to be excessive (above 6-7%), or efficacy insufficient, or if the natural history of patients referred to endovascular services is benign (risks below 3% over five years), clinicians may in the future become reluctant to offer this alternative to patients with unruptured lesions, and iatrogenia will be prevented. Conversely, a preventive strategy shown to be relatively safe may be an appropriate way to diminish the morbidity and dependency resulting from aneurysmal ruptures. Such a trial may have a strong impact on the clinical management of patients with unruptured aneurysms.

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Dr Jean Raymond, M.D.
CHUM Notre-Dame Hospital
Interventional Neuroradiology
1560 Sherbrooke east, suite M-8203
Montreal, Quebec, CANADA H2L 4M1
E-mail: dr_jean_raymond@hotmail.com