Clinical Trial Update

Unruptured intracranial aneurysms and the Trial on Endovascular Aneurysm Management (TEAM): The principles behind the protocol.

Jean Raymond, MD;[1] Daniel Roy, MD;[1] Alain Weill, MD;[1] François Guilbert, MD;[1]
Thanh Nguyen, MD;[1] Andrew J. Molyneux, MD;[2] Allan J. Fox, MD;[3] S. Claiborne Johnston, MD;[4]
Jean-Paul Collet, MD, PhD;[5] Isabelle Rouleau, PhD[6]
and the Trial on Endovascular Aneurysm Management (TEAM) collaborative group.

[1]Interventional Neuroradiology Research Unit, Université de Montréal, Canada
[2]Neurovascular Research Unit, Nuffield Department of Surgery, University of Oxford, United Kingdom
[3]Department of Medical Imaging, Sunnybrook Health Sciences Centre, Ontario, Canada
[4]Department of Neurology, University of California, San Francisco, USA
[5]Centre for Healthcare Innovation and Improvement, University of British Columbia, Vancouver, Canada
[6]Centre de Neurosciences de la Cognition, Université du Québec à Montréal, Canada

Abstract

Background: With the widespread availability of non-invasive imaging of the brain in an aging population, we are increasingly confronted with the problem of the incidental discovery of unruptured aneurysms. The management of these patients remains controversial. Endovascular treatment can prevent rupture, but involves immediate risks. Furthermore, successful treatment does not eliminate all risk of rupture. The safety and efficacy of endovascular treatment of unruptured aneurysms remain undetermined. Hence the balance of the risks and benefits is uncertain. A randomized trial is needed to assess the potential benefits of endovascular management of unruptured aneurysms.

The Trial: TEAM (Trial on Endovascular Aneurysm Management) is a randomized trial comparing endovascular treatment versus conservative management of unruptured aneurysms. TEAM aims to recruit 2002 patients in 60 centers throughout the world over a 3-year period and to follow all patients for 10 years. The primary outcome is to verify if the clinical outcome (morbidity/mortality (modified Rankin scale > 2) related to the aneurysm or its treatment) can be improved from 8% to 4%. The study is funded by the Canadian Institutes of Health Research.

Key words: unruptured aneurysm, TEAM, endovascular

J Vasc Interv Neurol 2008; 1(1)21-25

Correspondent: *Dr Jean Raymond; CHUM – Notre-Dame Hospital; Interventional Neuroradiology (NRI); 1560 Sherbrooke East, suite M8203; Montreal, Quebec, CANADA H2L 4M1; dr_jean_raymond@hotmail.com*

Abbreviations, in the order used in this report.

TEAM:	Trial on Endovascular Aneurysm Management
ISUIA:	International Study of Unruptured Intracranial Aneurysms
SF-36:	Standard Form 36
HADS:	Hospital Anxiety And Depression Scale

The Problem

The best management of patients with asymptomatic intracranial aneurysms is currently uncertain. The prevalence of intracranial aneurysms has been estimated at 1-2% of the adult population[1,2] but with the increasing availability of non-invasive imaging of the brain in an aging population, unruptured aneurysms are being discovered more frequently. Most aneurysms remain asymptomatic until the day they rupture, an event that occurs with an annual incidence of 8-10/100,000 in the overall population.[3-5] Subarachnoid haemorrhage is associated with a high morbidity and mortality (45-75%) despite the advances of modern surgical and medical management.[6-9] Thus a preventive treatment strategy is appealing.[9-21] The annual risk of bleeding from an unruptured aneurysm is debated, but most series and meta-analyses have reported a small annual risk, between 0.5-2%[2,15,22-29] with major morbidity or death affecting up to 60% of those patients with eventual ruptures.[29] Therefore, any preventive treatment should ideally be very safe and effective in preventing future rupture.

Endovascular treatment can prevent rupture but involves immediate risks to the patient.[16,30-37] Furthermore, successful treatment does not eliminate all risks.[30] Hence, the balance of the risks and benefits is uncertain. Nevertheless coiling of unruptured aneurysms is becoming the most frequent procedure performed in endovascular centres.[38]

The clinical dilemma, 'Are patients with unruptured aneurysms best managed conservatively or with active treatment?' can only find resolution by resorting to the rigorous methodology of the randomized clinical trial. This work cannot be delegated to a few scientists locked in their sophisticated laboratories. Clinical research is a science to be performed within real-world practice, and its success depends on the dedication of clinicians and the autonomous participation of subjects. Over decades, physicians have learned to deal with the complexity and diversity of this condition on a case by case basis, and have developed a unique expertise in approaching the most challenging situations. However, we have failed to provide justification for the preventive treatment of unruptured lesions.

The present manuscript proposes to review principles behind the TEAM trial's methodology, highlighting that they are based on strong moral and rational intuitions. We also hope to resolve some of the tensions involved in participating in the clinical trial designed to address the present dilemma.

The Research Question

Confronted with an apparently insurmountable clinical dilemma, one way to deceive oneself is to succumb to expediency and look for the wrong answer to the wrong question. The search for the so called 'natural history' of the disease has stirred the neurological community for decades. The immediate appeal of this approach is that it did not require the effort of randomization. These poorly-justified beliefs of clinical care specialists were so entrenched within the community that randomization was perceived as difficult, if not impossible.[39] The quest for the natural history of a disease cannot be approached as in the ISUIA study; i.e., that clinicians would attempt to study aneurysms at the same time they would continue to treat those patients they believe should be treated (because hemorrhagic risks were believed to be too high and treatment risks acceptable) and observe those patients they believe should not be treated (because hemorrhagic risks were believed to be too low or surgical risks too high) would automatically invalidate any comparison that one would attempt to make at the end of the study.[29] Once we obtain the 'natural history' of patients we did not want to treat, we realize after decades of collecting data that we are left empty handed. No one knows what would have been the natural history of patients that were treated.

As soon as one acknowledges that the reason for collecting so-called 'natural history' data was to guide clinical decisions regarding treatment, one realizes that the only reliable way of providing evidence for one treatment option or another is a randomized comparison. The perceived clinical reluctance to randomize treatment options despite the absence of evidence should only serve to emphasize how inescapable randomization is because this reluctance is a reliable indicator of how much bias exists in the minds of the clinical community, and how flawed our evaluation of 'natural history' will be if we try to resort to such a research strategy.

We have been treating and continue to treat an increasing number of patients with unruptured aneurysms. The pertinent question is not 'What is the natural history of an imaging finding?', because this is an illusive objective that depends on utilization of imaging equipment, selection of cases, and dubious methodology.[40] The pertinent question becomes: 'Are patients with unruptured aneurysms better off with conservative or interventional management?' A valid answer to this question can only come from the randomized trial methodology.

The Ethics of Randomization

We cannot reliably compare the outcome following two treatment options without resorting to randomization. This does not mean that we are bending the therapeutic obligation to individuals in a trial to meet the scientific requirements that will provide knowledge to guide the treatment of future individuals. The research question concerns first and foremost our current patients, for whom no action has yet been proven beneficial. Thus randomization is not only a scientific solution to the problem of bias; it is also a practical way of assuring the best possible outcome for each current individual patient.

While treating aneurysms before they rupture makes intuitive sense, no one has shown that by doing so we are doing more good than harm. Hence, we are uncertain about the best management in this situation and until we have evidence that treating aneurysms before they rupture leads to improved outcomes, the best option we can offer to individual patients is a chance to be protected from hemorrhage (by treating the aneurysm) and an equal chance to be exempted from the immediate complications of treatment. This calls for a one to one randomized allocation of two treatment options, one of them being conservative, exempt from surgical risks. This does not mean that physicians have no beliefs or hopes that their medical and surgical expertise is of value to patients. Of course physicians believe that what they do is for their patients' good. But in the spirit of modern medicine, physicians understand there is a substantial risk of iatrogenia (medicine has been wrong before); they recognize the need to provide evidence before recommending a risky preventive treatment and thus they are willing to subject their beliefs to the test of experience.

The necessity for a proof of benefit is a fundamental ethical requirement. Prevention is justified when risks of treatment are low and when benefits have been supported by valid trials. While medicine only has an obligation of means,[41] prevention has an obligation of results, because prevention only offers potential benefits and exposes healthy individuals to a certain risk.[41]

For those who still feel uncomfortable with the concept of uncertainty and the randomization process, it may be helpful to remember that at the end of the study period they will have been right in being uncertain about the best option for most patients, since for the overwhelming majority of participants (94%) the outcome will have remained unchanged at 10 years (see study hypotheses below).

Randomization is not giving up the decision to chance. It is to opt for a rational, responsible choice, to suspend judgment until there is evidence, to maximize chances of a benefit for each individual patient while we remain uncertain, and to act in a context that will promote knowledge and progress, in the respect of patient autonomy.

The Selection Criteria

Trials are often described as 'explanatory' or 'management' trials.[42] An explanatory trial is a selective process that aims at identifying potential benefits of a treatment in ideal conditions (restrictive eligibility criteria; optimal therapeutic conditions administered by selected experts; intense if not artificial monitoring; restricted outcome events). Once a therapy has become common practice the explanatory type of trial is no longer a practical option. Only an ambiguous conclusion could come from an explanatory trial that shows clear benefits for a very specific category of patients, while a management trial would prove that it is clearly worthwhile to adopt the treatment (or not). If we keep in mind the purpose of our investigation ('Is the outcome of patients with unruptured aneurysms improved with treatment as compared with observation?'), we shall opt for the 'management' type of trial. This calls for a large, simple trial, looking for a pragmatic answer (1) with loose eligibility criteria based on uncertainty, (2) taking all comers (3) retaining every admitted patient in the analysis, (4) proceeding with non-obstructive monitoring, (5) ascertaining a range of hard, well-defined outcome events, and (6) counting every event and charging it against intervention (Table 6-4, page 185 in reference 42).

So who are the patients to be included in the trial? The short answer is any patient currently considered for endovascular treatment. There may be occasions where risks of hemorrhage are thought to be increased if the lesion is left untreated (large or posterior circulation aneurysms, for example). These circumstances have however also been associated with increased treatment risks and risk for aneurysm recurrence after treatment.[29] Thus the best treatment remains uncertain.

Primary Endpoints, Sample Size and Observation Period

The primary endpoint of a trial must answer the research question with pertinence. The answer must be meaningful and convincing to the relevant community. Endpoints should be easy to ascertain rigorously, credible to clinicians, resistant to bias, and provide evidence likely to impact on practices.

When blinding is not possible, it is judicious to choose a 'hard' outcome, less sensitive to bias, such as overall mortality. Although hemorrhagic events in patients with unruptured aneurysms may be infrequent, death is a common consequence.[29] Hence the trial has been powered to detect a difference in overall mortality between two groups. One difficulty is that with a sufficiently long trial, eventually everyone dies. In addition, many patients fear dependency more than they fear death, and treatment may cause more morbidity than mortality, though the overall risk of either event is low.[14] Thus by treating unruptured aneurysms we may be trading mortality for dependency. Alternative possibilities for choosing the outcome events of a trial is overall morbidity and mortality, or that caused by the lesion or its treatment, but blind adjudication by an independent committee becomes mandatory.[42]

Sample size is determined according to hypotheses and statistical rules, with care to control the type I error for the primary outcome event. What actually determines the size of the population to be studied is the number of outcome events, which must first be estimated. The smaller the number of events, the larger the population needed to show a significant difference between two groups. We have used the observational data from Wermer[2] and ISUIA[29] to estimate the morbidity of conservative management, with 8% morbidity at 10 years. The pre-defined estimates for treatment risks are compatible with the recent multicentric French registry on endovascular treatment of unruptured aneurysms,[37] which reported a 3% morbidity and mortality (modified Rankin scale > 1), leaving only a 1% residual hemorrhagic risks despite treatment for the entire follow-up period.

Sample size determination is often performed in a pragmatic fashion; a number of patients that is feasible to recruit is first estimated, and the investigators evaluate a difference between two groups that would be clinically significant. This statistical process can only determine the size necessary to claim that the differences observed are unlikely to be caused by chance alone. This crucial step often turns out to be a humbling experience, as one realizes the limits of clinical research. We cannot design a trial that would provide answers specific to all subgroups that may be of interest.

The duration of a meaningful follow-up period must also be selected with care. This is obvious when one studies 'cures' after cancer treatment. There are a number of illicit assumptions that are hidden behind the choice of an observation period in research concerning aneurysms. Is the risk of rupture constant with time, age, smoking, or concomitant diseases? Of course we have no definite answer to this problem, but we should think in these terms: What would be clinically meaningful once we want to apply our new knowledge to our clinical decisions? Obviously treatment entails immediate risks, a price to pay in exchange for future protection from hemorrhage. The observation period must be sufficiently long to allow treatment to show its potential benefit. Since the information we want is such that it could apply to the patients in need of immediate care (patients with the clinical dilemma of preventively treating their aneurysm or not), a safe choice is an observation period that is long, in the range of 10 years. It is in patients with a relatively long life expectancy, walking around and working, in which treatment would be considered.

The Proposed Trial

TEAM is an international, randomized, multicenter, controlled trial comparing the combined mortality and morbidity (modified Rankin scale > 2) from intracranial hemorrhage or treatment in patients with unruptured aneurysms treated by conservative management (or deferral of treatment for 10 years or until definite indications are thought to have arisen) as compared to endovascular coiling.

The study will be conducted in 60 international centers. The entire study will enrol 2002 patients equally divided between the two groups, a size sufficient to achieve 80% power at a 0.0167 significance to detect differences in (1) disease or treatment-related poor outcomes from 7-9% to 3-5% as judged by an independent committee masked to treatment allocation and (2) overall mortality from 16% to 11%. The duration forecast for the study is 14 years, the first 3 years being for patient recruitment plus a minimum of 10 years of follow-up.

Secondary end points will include the incidence of hemorrhagic events in both groups, the morbidity related to endovascular coiling, morphological results as assessed by non-invasive imaging at 5 and 10 years, overall clinical outcome at 5 and 10 years, quality of life assessment (SF-36), and the

level of distress caused by the knowledge of the hemorrhagic risk using the HADS questionnaire.

Other details of the research protocol can be found at www.TEAMstudy.org

Other Treatment Strategies and Other Trial Designs

Surgical clipping of unruptured aneurysms is a treatment option that would also require validation of its benefit. Surgical clipping will be explained and consulting for this option offered to all study participants. Patients indisputably necessitating surgery are not eligible. Which treatment is better, surgical clipping or coiling, is not a question that the current trial will be able to answer. A single trial cannot answer all questions. Our opinion is that physicians offering surgical clipping should also proceed with a randomized trial to prove that the proposed intervention is in general beneficial to patients with unruptured aneurysms.

We have carefully considered including a surgical arm to our research effort. Reasons for excluding this design are numerous and cannot be discussed in detail in the current article. Randomization to three groups (endovascular, surgical, conservative) necessitates restricting entry to patients in whom three very different options – with a wide range of risks, degrees of invasiveness, and efficacy – are felt to be equally appropriate, is a difficult concept to grasp for most physicians and patients. By definition the trial would only address the intersection of three categories of patients, leaving the majority outside the realm of scientific evaluation, with very little possibility of generalizing results beyond a narrow range of patients at the end of a long trial.

A trial comparing conservative management with 'treatment' (endovascular, surgical, or both) could come in various flavours. It is difficult to conceptualize what would be the nature of such an artificially unified 'treatment'. A predetermined set of criteria could be used to select endovascular or surgical options, but besides rare exceptions, it is impossible to provide consensual criteria (that by necessity would be arbitrary) agreeable to a majority of experts of different backgrounds. In addition, this procedure is like putting the cart in the front of the horse: What would be the credibility of deciding a priori, before the onset of a trial designed to show the benefits a certain treatment, for whom this or that particular treatment is beneficial? The decision regarding 'treatment' choices could be left to the local teams, but then one should not expect that the various communities of experts will understand and accept the verdict of the trial at the end of a long research endeavour. It is of the outmost importance that a pragmatic trial be designed in such a fashion as to offer compelling justification for a generalizable guide to clinical decisions, credible to the experts of the relevant communities. When two treatment options vastly different in complications rates and long term efficacy are lumped into a single unified 'treatment,' we no longer understand what is being studied. In addition, the primary hypotheses, determination of a clinically meaningful sample size and observation period, trial monitoring, stopping rules, relevance and significance of results are important conceptual aspects of the trial that become virtually impossible to interpret. The meaning of the trial becomes ambiguous.

The answer to the research question must convincingly replace the current uncertainty, and the community of experts should be willing to 'shift' its core beliefs according to results of the trial. A trial comparing conservative management with 'treatment' of any kind can only be thinkable when one has an a priori prejudice in favour of conservative management. But why should physicians and patients take risks and spend 10-15 years to demonstrate that therapy is harmful? Most people believe that what they do is for the benefit of patients, but they are uncertain. Then the fundamental principle of prudence forces physicians to submit their beliefs to the verdict of experience. A trial must be designed to allow an optimistic perspective to be either confirmed or refuted by credible evidence.

Conclusion

Endovascular treatment is an established means of treating intracranial aneurysms. An objective assessment of its value in unruptured aneurysms is now imperative. A randomized trial can reconcile the continued use of an established therapy with the necessity of acknowledging current uncertainties, the need to scientifically assess potential benefits, and to assist healthy individuals alerted by the discovery of an ominous condition, in a controlled environment that respects and promotes their autonomy.

References

1. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, Niessen WJ, Breteler MM, van der Lugt A. Incidental findings on brain MRI in the general population. N Engl J Med 2007;357(18):1821-1828.
2. Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke 2007;38:1404-1410.
3. Menghini VV, Brown RD, Jr., Sicks JD, O'Fallon WM, Wiebers DO. Incidence and prevalence of intracranial aneurysms and hemorrhage in Olmsted County, Minnesota, 1965 to 1995. Neurology 1998; 51:405-411.
4. Meyer FB, Morita A, Puumala MR, Nichols DA. Medical and surgical management of intracranial aneurysms. Mayo Clin Proc 1995; 70:153-172
5. Rinkel GJ, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: A systematic review. Stroke 1998; 29:251-256
6. Broderick JP, Brott TG, Duldner JE, Tomsick T, Leach A. Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. Stroke 1994; 25:1342-1347
7. Kassell NF, Torner JC, Haley EC, Jr., Jane JA, Adams HP, Kongable GL. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. J Neurosurg 1990; 73:18-36.
8. Ropper AH, Zervas NT. Outcome 1 year after SAH from cerebral aneurysm. Management morbidity, mortality, and functional status in 112 consecutive good-risk patients. J Neurosurg 1984; 60:909-915
9. Rasmussen P, Mayberg M. Defining the natural history of unruptured aneurysms. Stroke 2004; 35:232-233.
10. Chang HS, Kirino T. Quantification of operative benefit for unruptured cerebral aneurysms: A theoretical approach. J Neurosurg 1995; 83:413-420.
11. Kassell N, Lanzino G. Unruptured intracranial aneurysms: In search of the best management strategy. Editorial comment. Stroke. 2001; 32:603-605.
12. King JT, Jr., Berlin JA, Flamm ES. Morbidity and mortality from elective surgery for asymptomatic, unruptured, intracranial aneurysms: A meta-analysis. J Neurosurg 1994; 81:837-842.
13. Leblanc R, Worsley KJ. Surgery of unruptured, asymptomatic aneurysms: A decision analysis. Can J Neurol Sci 1995; 22:30-35.
14. Raaymakers TW, Rinkel GJ, Limburg M, Algra A. Mortality and

morbidity of surgery for unruptured intracranial aneurysms: A meta-analysis. Stroke 1998; 29:1531-1538.
15. van Crevel H, Habbema JD, Braakman R. Decision analysis of the management of incidental intracranial saccular aneurysms. Neurology 1986; 36:1335-1339
16. Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC, Jr., Brott T, Hademenos G, Chyatte D, Rosenwasser R, Caroselli C. Recommendations for the management of patients with unruptured intracranial aneurysms: A statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke 2000; 31:2742-2750.
17. Khanna RK, Malik GM, Qureshi N. Predicting outcome following surgical treatment of unruptured intracranial aneurysms: A proposed grading system. J Neurosurg. 1996;84:49-54
18. Juvela S. Unruptured aneurysms. J Neurosurg 2002; 96:58-60.
19. Juvela S, Hernesniemi J. Clinical manifestations and survival rates among patients with saccular intracranial aneurysms: Population-based study in Olmsted County, Minnesota, 1965 to 1995. Neurosurgery 2002; 50:1167-1169.
20. Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: Probability of and risk factors for aneurysm rupture. J Neurosurg 2000; 93:379-387.
21. Wiebers D. Unruptured intracranial aneurysms - risk of rupture and risks of surgical intervention. The International Study of Unruptured Intracranial Aneurysms investigators. New England J Med. 1998; 339:1725-1733.
22. Asari S, Ohmoto T. Natural history and risk factors of unruptured cerebral aneurysms. Clin Neurol Neurosurg 1993; 95:205-214.
23. Brennan JW, Schwartz ML. Unruptured intracranial aneurysms: Appraisal of the literature and suggested recommendations for surgery, using evidence-based medicine criteria. Neurosurgery 2000; 47:1359-1372.
24. Graf CJ. Prognosis for patients with nonsurgically-treated aneurysms. Analysis of the Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage. J Neurosurg 1971; 35:438-443.
25. Juvela S. Natural history of unruptured intracranial aneurysms: Risks for aneurysm formation, growth, and rupture. Acta Neurochir Suppl 2002; 82:27-30.
26. Tsutsumi K, Ueki K, Morita A, Kirino T. Risk of rupture from incidental cerebral aneurysms. J Neurosurg 2000; 93:550-553.
27. Weir B. Unruptured intracranial aneurysms: A review. J Neurosurg 2002; 96:3-42.
28. Weir B, Disney L, Karrison T. Sizes of ruptured and unruptured aneurysms in relation to their sites and the ages of patients. J Neurosurg 2002; 96:64-70.
29. Wiebers DO, Whisnant JP, Huston J, 3rd, Meissner I, Brown RD, Jr., Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC: International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: Natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 2003; 362:103-110.
30. Raymond J, Guilbert F, Weill A, Georganos SA, Juravsky L, Lambert A, Lamoureux J, Chagnon M, Roy D. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. Stroke 2003; 34:1398-1403.
31. The CARAT Investigators. Rates of delayed rebleeding from intracranial aneurysms are low after surgical and endovascular treatment. Stroke 2006; 37:1437-1442.
32. Goddard AJ, Annesley-Williams D, Gholkar A. Endovascular management of unruptured intracranial aneurysms: Does outcome justify treatment? J Neurol Neurosurg Psychiatry 2002; 72:485-490.
33. Kanashiro L, Campos C, Abicalaf R, Baccin C, Fonseca N, Lima S, Piske R. Incidental cerebral aneurysms: Endovascular treatment. Interventional Neuroradiology 2003; 9:162.
34. Lemme-Plaghos L, Garbugino S, Casagrande W, Van Ooteghem M. Endovascular treatment of incidental aneurysms with GDC coils. Interventional Neuroradiology 2003; 9:162.
35. Murayama Y, Vinuela F, Duckwiler GR, Gobin YP, Guglielmi G. Embolization of incidental cerebral aneurysms by using the Guglielmi detachable coil system. J Neurosurg 1999; 90:207-214.
36. Roy D, Milot G, Raymond J. Endovascular treatment of unruptured aneurysms. Stroke 2001; 32:1998-2004.
37. Pierot L, Spelle L, ATENA investigators. Preliminary results of the ATENA study regarding the endovascular treatment of unruptured intracranial aneurysms. Interventional Neuroradiology 2007; 13(Suppl 2):49.
38. Cowan JA Jr, Ziewacz J, Dimick JB, Upchurch GR Jr, Thompson BG. Use of endovascular coil embolization and surgical clip occlusion for cerebral artery aneurysms. J Neurosurg 2007; 107:530-535.
39. Sackett DL. The arrogance of preventive medicine. CMAJ. 2002;167:363-364.
40. Raymond J, Roy D, Weill A, Guilbert F, Nguyen T, Molyneux AJ, Fox AJ, Johnston SC, Cognard C, Pierot L, Meder JF, Rouleau I and the *Trial on Endovascular Aneurysm Management (TEAM) collaborative group. Unruptured Intracranial Aneurysms: Their illusive natural history and why subgroup statistics cannot provide normative criteria for clinical decisions or selection criteria for a randomized trial. J Neurorad (in press).
41. Tubiana M. Histoire de la pensée médicale. Les chemins d'Esculape. Flammarion, Paris 1995.
42. Haynes BR, Sackett DL, Guyatt GH, Tugwell P. Clinical epidemiology: How to do clinical practice research. 3rd edition; Lippincott, Williams and Wilkins; Philadelphia 2006.