UNRUPTURED INTRACRANIAL ANEURYSMS: THE UNRELIABILITY OF CLINICAL JUDGMENT, THE NECESSITY FOR EVIDENCE, AND REASONS TO PARTICIPATE IN A RANDOMIZED TRIAL


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"It is impossible for a man to learn what he thinks he already knows"  
Epictetus

The best management of patients with asymptomatic intracranial aneurysms is currently uncertain. The prevalence of intracranial aneurysms has been estimated at 1 to 5% of the adult population [1] but with the increasing availability of non-invasive imaging of the brain in an aging population, unruptured aneurysms are increasingly being discovered. 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 [2-4]. Subarachnoid haemorrhage (SAH) is associated with a high morbidity and mortality (45-75%) [5-7] despite the advances of modern surgical and medical management [6, 8]. Thus a preventive treatment strategy is appealing [1, 8-14]. The annual risk of bleeding from an unruptured aneurysm is debated, but most series and meta-analysis have reported a small annual risk, between 0.05-2% [14-21] with major morbidity or death affecting up to 60% of those patients with eventual ruptures [22]. Any preventive treatment should therefore be very safe.

Prevention is justified when risks of treatment are low and when benefits have been supported by valid trials[CJ1]. While medicine only has an obligation of means[CJ2], prevention has an obligation of results, because prevention only offers potential benefits and exposes healthy individuals to a certain risk [1, 23]. It is clear from these principles that in the management of unruptured aneurysms the conditions for preventive actions have not been met. The puzzle is: why do we treat UIAs so frequently? Possible answers will be explored here, and the potential weaknesses of our current clinical attitude that we will uncover will be emphasized in an effort to promote participation in a clinical trial. Reasons for the trial, and crucial knowledge that such a trial would provide, will be numbered and outlined by propositions written in italic characters.

(1) A randomized trial is in order to support the claim that endovascular treatment is in general beneficial to patients with unruptured intracranial aneurysms. TEAM (Trial on Endovascular Aneurysm Management) was designed to provide a rational basis to the preventive endovascular treatment of aneurysms; it is a randomized, multi-centre, controlled study comparing the mortality and morbidity in patients with unruptured aneurysms treated by conservative management or endovascular coiling.

THE FACTS

The fact is that we have no reliable data on the risk of haemorrhage associated with an incidental intracranial aneurysm, and we have no reliable evidence of the efficacy of treatment.

Risk of haemorrhage versus risk of treatment

Most recent evidence on the relative risks of treatment and on the risks of observation comes from the International Study on Unruptured Intracranial Aneurysms (ISUIA) [22].

It seems that the logic behind the design of ISUIA was to attempt to collect information on the incidence of rupture and on treatment risks
SURGICAL, ENDOVASCULAR, OR CONSERVATIVE MANAGEMENT?

There is currently no scientific evidence to support surgical or endovascular treatment of unruptured aneurysms and no well-accepted guidelines [32]. 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” [20]. Continuous efforts at identifying subgroups of patients with higher risks of rupture to target a population in which treatment may be indicated has unfortunately been confronted by the fact that a high-risk natural history is often associated with a high surgical risk [22, 33].

Many 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 [8, 10, 34-36]. Other groups, often led by neurologists, believe that more than a lifetime of rupture risk is taken by operating on patients with unruptured lesions [22, 32, 37, 38]. In the meantime clinicians rely on “clinical judgment”, using various homemade algorithms, taking into account age, size, location of aneurysms, the patient’s attitude toward knowing they have an untreated aneurysm, as well as an “honest” assessment of neurosurgical skills, limitations and complications [39]. Unfortunately this decision-making process is heavily influenced by the clinician’s culture and personality.

CLINICAL JUDGMENT

It is easier for physicians to grant themselves the power of omniscience in deciding what is best for the patient than to recognize the limitations of their own knowledge. However, omniscience has never been a requirement of medical practice. “After all, persons are licensed as physicians because they have validated knowledge, not after they reveal superior capacity for guessing” [40].

There is considerable evidence that faced with difficult problems, beliefs and preferences are often constructed, not merely revealed [41]. Construction strategies include anchoring our beliefs on reference points and adjustment according to perceived differences, relying on the prominent dimension, eliminating common elements, discarding nonessential differences, restructuring the problem to create dominance and thus reduce conflicts and indecision. The mental gymnastics is a highly contingent form of information processing, sensitive to complexity, time pressure, framing, and numerous other contextual factors [42].

Besides unreliable evidence, there are many other reasons why we should be wary of our current beliefs on unruptured aneurysms. Some are motivational. These include distortions of judgment caused by pay-offs and penalties. It is difficult to evade the fact that we get paid for treating aneurysms. Others
could be called emotional: the fear of the hemorrhagic event, or the potential regret or guilt that would occur after a hemorrhagic event, had we left the patient untreated. There is also pressure from peers and "corporative thinking": we are a collection of experts, with unique skills in the treatment of aneurysms, trained to think in a certain sort of way. Realism and pessimism about what we can do can readily be interpreted as disloyalty and bearers of bad news would tend to be shunned.

Perhaps more importantly, there is strong evidence that decision making under uncertainty is performed according to heuristics (processes allowing to learn by ourselves) that are liable to systematic errors and biases, that are shared by laymen and experts, pervasive under a wide array of conditions, and persistent and resistant to evidence and education [41]. Knowledge of the cognitive processes involved in decision making under uncertainty may be essential to avoid potential pitfalls.

### Decision under uncertainty

Expected utility theory (that assumes that decision makers will act according to rules that will maximize benefits) reigned for several decades as the dominant normative model of decision making under uncertainty. There is now general agreement that the theory does not provide an adequate description of what goes on in individual choices. Decision makers systematically violate its basic tenets.

In some situations the normative and the positive theories coincide. If a problem is sufficiently simple the normative theory will be acceptable. But what about more complicated situations that call for sophisticated notions like probabilities?

For example the famous birthday problem in statistics illustrates the non-intuitive nature of probabilities. If 25 people are in a room, what is the probability that at least one pair will share a birthday? This problem is famous because everyone guesses wrong when he first hears it. Furthermore the error is systematic, everyone guesses too low (the correct answer is greater than 0.5). The problem is a form of mental illusion and research on decision making under uncertainty has shown that such mental illusions is the rule rather than the exception [43]. Although observational studies remain to be performed in our field, we suspect that the "deep intuitions" that many physicians feel regarding the treatment of aneurysms have to do with such illusions and irrational heuristics that we will briefly review now.

### Framing and weighting value function

The expression of preference by means of choice and decision making is the essence of intelligent, purposeful behaviour. The first formal theories assumed that decision makers are completely informed about the possible courses of action and their consequences, infinitely sensitive to differences in alternatives, and rational in the sense that they can order possible choices and make decisions that maximize subjective measure of value or welfare usually designated by the term utility [44].

This idealized context is hardly ever encountered in clinical practice.

Preferences appear to be remarkably labile, sensitive to the way a choice problem is described or "framed". The framing effect occurs when two formulations of the same problem elicit different preferences. A basic assumption of rational theories of choice is the principle of invariance, which states that the relation of preference should not depend on the description of the options or on the method of elicitation. Because the framing effect and the associated failures of invariance are ubiquitous, no one can ignore these phenomena. We know that public perception of the frequency of risks can be systematically biased. For example, risks associated with vivid causes that killed many people in a single occurrence are overestimated, while less vivid causes of death such as most common diseases are systematically underestimated [45]. Liability to bias is not limited to the public however.

The reliance on clinical judgment, also susceptible to framing, often leads to violations of rationality, and of the invariance principle (table I). Many of these violations can be explained by a non-linear weighting function of values that overweights low probabilities and underweights moderate to high probabilities. The function is not well-behaved near the endpoints, and very small probabilities can be either greatly

**Table I** - This example is meant to illustrate the effect of framing on decision under uncertainty. Many would choose treatment A over B, but D over C, and very little added morbidity would be acceptable when choosing E over F. But of course A=C=E while B=D=F. Please also notice that numbers are compatible with published rates for surgical (A) or endovascular (B) treatment of aneurysms.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mortality/morbidity</th>
<th>Life expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15% risks</td>
<td>0% of patients at risk of bleeding after;</td>
</tr>
<tr>
<td>B</td>
<td>8% risks</td>
<td>10% of patients at risk of bleeding after;</td>
</tr>
<tr>
<td>C</td>
<td>15% risks</td>
<td>0% of patients at risk of bleeding after;</td>
</tr>
<tr>
<td>D</td>
<td>8% risks</td>
<td>10% of patients at risk of bleeding after;</td>
</tr>
<tr>
<td>E</td>
<td>15% risks</td>
<td>0% of patients at risk of bleeding after;</td>
</tr>
<tr>
<td>F</td>
<td>8% risks</td>
<td>10% of patients at risk of bleeding after;</td>
</tr>
</tbody>
</table>

**Framing effect:**

There are 100 patients with an unruptured intracranial aneurysms (all the same; for example an anterior communicating artery aneurysm 8 mm in size)

1. Choose between 2 treatments of such intracranial aneurysm in 100 patients:
   a. Treatment A=15% risks of treatment; 0% of patients at risk of bleeding after;
   b. Treatment B=8% risks of treatment; 10% of patients at risk of bleeding after;

2. Choose between 2 treatments of such intracranial aneurysm in 100 patients
   a. Treatment C=Fifteen patients have a permanent morbidity/mortality from treatment; 85 patients have a normal life expectancy in normal condition
   b. Treatment D=Eight patients have a permanent morbidity/mortality from treatment; 83 patients have a normal life expectancy in normal condition

3. In how many more patients are you willing to cause a permanent morbidity immediately using a treatment E to protect 85% instead of 83% of patients with treatment F?
overweighted or neglected altogether [46]. Perhaps the way we behave is reminiscent of some adaptive mechanisms: organisms habituate to steady states, the marginal response to changes is diminishing and pain is more urgent than pleasure.

Overweighting of small probabilities contribute to both lotteries and insurance, and perhaps to the systematic treatment of small unruptured aneurysms. Underweighting of high probabilities contributes to the prevalence of risk aversion in choices between probable gains and sure things and to prevalence of risk seeking in choices between probable and sure losses, even though the “sure things” and “sure losses” may also be only apparent or “framed”. An event has more impact on choice when it turns impossibility into a possibility or a possibility into a certainty than when it merely makes a possibility more or less likely. This effect can be dramatically demonstrated in people who, when asked how much they would be willing to pay to remove one bullet in a faked game of Russian roulette, are prone to pay much more for the last bullet than for any other [47]. This effect is more pronounced for uncertainty than for risk, indicating greater departure from expected utility theory when probabilities are not known. Perhaps these distortions of risk perceptions could explain how surgical clipping, often labeled as “curative”, could be preferred to coiling, although it implies added immediate risks.

Ambiguity versus risks

One fundamental problem is the analysis of judgment under ignorance or ambiguity, where the probabilities of potential outcomes are neither specified nor readily assessed on the basis of available evidence. And this is the present context in decision making regarding UIAs.

The frequently observed preference of decision makers to bet on clear or known probabilities rather than vague or unknown probabilities has been called ambiguity aversion [48]. It would seem rational to base our decisions on the treatment of aneurysms on well defined probabilities rather than on vague intuitions. Although people exhibit ambiguity aversion in situations of complete ignorance, they sometimes prefer to bet on their vague beliefs than on matched chance events. This may be the case with clinical judgment. The evidence is consistent with a more general account, called the competence hypothesis: people prefer to bet on their vague beliefs in situations in which they feel particularly competent or knowledgeable, and they prefer to bet on chance when they do not [49].

Unfortunately reliance on vague beliefs paves the way to systematic error that may translate into clinical morbidity. If ambiguity aversion is driven by the feeling of incompetence, the question arises as to what conditions produce the feeling of competence, in the mind of physicians, given the uncertain and widely discordant probabilities that have been associated with unruptured aneurysms.

Overconfidence and Control

Most individuals believe themselves to be above average, and very few would judge themselves below average. But half must be. Unfortunately experts, once they are forced to go beyond their data and rely on judgment, may be as prone, if not more, to overconfidence as lay people. Thus calibration of physicians [47], in the few studies available, was abysmal [50].

People also exaggerate their control over events, and the importance of skills and resources they possess in ensuring a desirable outcome. The illusion of control is motivated by a will to control or master one’s environment, but most cannot discriminate between controllable and uncontrollable events. While an emphasis on the control possible in preventing complications of the procedure seems healthy in teaching neurointerventional techniques, one should also teach that there are limitations to our abilities to control clinical events.

Taylor and Brown reached the disturbing conclusion that optimistic self-delusion is both a marker of mental health and well-being, and a positive causal factor that contributes to successful coping with the challenges of life [51].

Facing the facts can be intolerably demoralizing. But given the high cost of mistakes, it might appear judicious that a rational expert should want to base his decision on unbiased odds rather than on predictions painted in shades of rose.

(6) A randomized controlled trial is the only antidote to rosy evaluations of our performance.

Decision, action and time sequences

Decisions of importance have delayed consequences. Empirical evidence suggests that delayed outcomes are valued less. Although in certain circumstances people like to defer desirable outcomes, getting undesirable outcomes over quickly appears to be more widespread. It seems that many physicians believe that patients would prefer to concentrate potential losses first in a single event and then spread the benefits over a long future.

Savouring and dread apply to single outcome prospects as well as to outcome sequences They can explain why people who otherwise discount the future sometimes defer pleasurable outcomes and get unpleasant outcomes over with quickly. Thus surgery could be viewed as a single undesirable event giving rise to a sequence of desirable events (here perhaps the recovery of “normal” life expectancy) [52].

But these preferences may lead to anomalies and an individual decision may be contrary to the patient’s self-interest. For example, losses are discounted with time at a lower rate than gains. In observational studies, many subjects actually exhibited negative discounting, in that they preferred an immediate loss over a delayed loss of equal value [53]. This type of behaviour may explain why people would choose a treatment that apparently entails more immediate risks than the estimate of the long-term probability of hemorrhagic events.

Opportunities for learning

The assumption of the rationality of decision making is often defended by the argument that people will learn to make correct decisions and sometimes by the evolutionary argument that irrational decision makers will be driven out by rational ones.

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Evidence indicates that people can spend a lifetime in a competitive environment without acquiring a general ability to avoid framing effects [53]. Effective learning takes place only in certain conditions: it requires accurate and immediate feedback about the relation between the situational conditions and the appropriate response. But the necessary feedback is often lacking: 1. outcomes are delayed and not easily attributable to a particular action; 2. variability in the environment affect the reliability of the feedback, especially when outcomes of low probability are involved; 3. there is often no information about what the outcome would have been if another decision had been taken and 4. many decisions are unique and therefore provide little opportunity for learning. (7) Only randomized clinical trials can provide long-term, accurate and valid feedback.

The claim that real life can be trusted to correct the effect of individual irrationalities cannot be made without supporting evidence. Heuristics are learned by repetition, inductively, with reinforcements. Because of the way “feedback” normally occurs, positive reinforcement can occur even for incorrect rules [54]. It has been observed that one can choose to act in such a way that learning is precluded. Perhaps this is what has been done in the past with unruptured aneurysms. Expert groups have exhibited a type of consensual thinking regarding the treatment of aneurysms. A consensus is not necessarily an indication of consensual thinking regarding the treatment of aneurysms. A consensus is not necessarily an indication of validity: a shared deficiency of reasoning will also yield a consensus, and it is exactly the characteristics of error-prone heuristics to be widely shared among decision makers.

Such a clinical behaviour could have been perceived as a privilege for expert groups: “In the land of the blind, the one-eyed man is king” (Erasmus) [55].

The patient is unique; the internal and external views

Decision makers are excessively prone to treat problems as unique. Physicians prefer to view risk as a challenge to be overcome by the exercise of skill, and choice as a commitment to a goal. Although they do not deny the possibility of error, they see themselves not as knowledgeable gamblers but as prudent and determined agents, who are in control of both people and events. They are in fact subject to the conflicting biases of unjustifiable optimism and unreasonable risk aversion. It is the denial of uncontrollable uncertainty that accounts for the physicians’ views of themselves as prudent risk takers [56]. One-at-a-time accounting combines with loss aversion to inflate error in economic decisions [43]. The antidote for excessive risk aversion is aggregation.

A decision maker who is risk averse in some situations and risk seeking in others ends up paying a premium to avoid some risks and a premium to obtain others. The results may be an irrational and excessive cost in terms of risks for most patients. Myopic discounting, as this behaviour is sometimes called in economic circles, can find an antidote, in the adoption of a broader frame and a consistent risk policy, if two conditions are met: an ability to group together problems that are superficially different and an appropriate procedure for evaluating outcomes and the quality of performance (according to Kahneman and Lovallo [56]). Both requirements are provided in the clinical trial scenario, in which individuals are considered as belonging to the class of patients who may benefit from treatment and in which carefully controlled and predetermined outcomes will provide the feedback necessary to gain reliable knowledge.

An inside-view forecast is generated by focusing on the case at hand, on knowledge of the specific details, likely obstacles and how they might be overcome. The intellectual detour into the statistics of related cases is seldom chosen spontaneously. The outside view, in contrast, focuses on the statistics of a class of cases chosen to be similar in relevant respects to the present one. It involves no attempt to divine future history [56] but relies essentially on statistics. The relevance of the outside view is sometimes explicitly denied, especially with physicians and lawyers, and the inside view is overwhelmingly preferred in intuitive forecasting. This preference sometimes bears a moral character. It is valued as a serious attempt to come to grips with the complexities of the unique case at hand [56]. This attitude can be costly in the terms of predictive accuracy, and in our field, in terms of morbidity.

The overall interests of each individual patient are better served by aggregating the problems than by segregating them, and by a policy that is generally more risk-neutral than intuitive individual preferences. (8) Such a policy can be provided by a randomized trial.

THE NEED FOR A RATIONAL PROCEDURE

If it is irrational to work according to error-prone heuristics, is it wrong?

Well it depends. If you make a living out of it, it is at least fair to ask the question. Experts who are aware of the propensity of their clients for distorted risk perception and secondary deleterious behaviours (such as selling stocks each time they are going down, buying when they are going up) are expected to advise them appropriately, and not take advantage of the deficiency of their judgments.

Clinical judgment, despite all these pitfalls, will always be necessary to apply available scientific evidence to the individual case at hand. But the evidence must first be available. The respect clinicians wish to manifest regarding the individual patient is illusory in a context liable to framing, in which information consists of vague beliefs, biased evidence, and over-confidence in one’s judgment and skills, and using error-prone cognitive processes in decision making [57].

A randomized trial can offer scientific evidence that treatment is in general effective and beneficial as compared to observation. Certain physicians may claim that they already know this, but we contend that only if a trial is positive, would it be a consolation to be right for the wrong reasons. A trial may offer less biased estimates of the immediate risks of treatment and of long-term risks of the incidental lesion.
without which a truly informed consent and respect for the patient’s autonomy are forever impossible. The way the problem has been put into perspective so far is bound to have been distorted, and the “equipoise” notion proposed by the randomized trial is closer to genuine respect for a “real preference” of the individual.

Perhaps more importantly, (9) until we get reliable evidence, randomization is the best way to optimize treatment outcome for each individual patient.

A RANDOMIZED TRIAL COMPARING ENDOVASCULAR TREATMENT WITH INDEFINITE DEFERRAL OF TREATMENT (TEAM)

The management of patients with unruptured aneurysms remains controversial. Patients with unruptured aneurysms may suffer intracranial haemorrhage, but the incidence of this event is still debated. Endovascular treatment can prevent rupture, but involves immediate risks. Furthermore, successful treatment does not eliminate all risks. The safety and efficacy of endovascular treatment of unruptured intracranial aneurysms remain undetermined. Hence the balance of the risks and benefits is uncertain. We are initiating an international, randomized, multi-centre, controlled trial comparing the combined mortality and morbidity (MRS ≥3) from intracranial haemorrhage in patients with unruptured aneurysms treated by conservative management (or deferral for 10 years or until definite indications are thought to have arisen) as compared to endovascular coiling.

Secondary endpoints will include the incidence of hemorrhagic events in both groups, the morbidity related to endovascular coiling, morphological results at 5 and 10 years, overall clinical outcome at 5 and 10 years, quality of life assessment, and the level of distress caused by the knowledge of the hemorrhagic risk. To take into account ease of recruitment, feasibility, generalizability, and ethical considerations, entry criteria will be minimized. The analyses will be performed on two populations: intent-to-treat and per protocol. The main statistical tests will involve comparisons between the 5- and 10-year probabilities of poor outcomes (MRS ≥3) 1/ from haemorrhage related to the lesion, excluding per operative complications), 2/the 5/10-year probabilities of mortality from haemorrhage or from complications of treatment, or 3/comparisons of the 5- and 10-year probabilities of combined disease or treatment-related mortality and morbidity, in the absence of other causes of death or disability. Other analyses will involve Kaplan-Meier life-table methods to assess the 5- and 10-year mortality from intracranial bleeding or from treatment among all those allocated immediate coiling (including the few who did not undergo it) and all those allocated deferral of any intervention (including the few who will eventually be operated on) as well as overall mortality. The study will be conducted in 60 international centres. The entire study will enrol approximately 2,002 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%; 2) overall mortality from 16 to 11%. The duration forecast of the study is 14 years, the first three years being for patient recruitment plus a minimum of 10 years of follow-up.

CONCLUSION

There is currently no scientific justification to treat unruptured aneurysms. A randomized trial can provide real progress. Recruitment and randomization of patients necessitate a change of mentality, but this effort is necessary. Genuine respect for subjects and human dignity requires that clinical research meets scientific norms of excellence. The use of subjects can only be justified when the objective of research is to provide unbiased results, and the golden rule to prevent biases is randomization. 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 benefit for each patient, and to act in a context that will promote knowledge. Once we have acquired reliable knowledge we are in a position to offer optimal care.

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UNRUPPED INTRACRANIAL ANEURYSMS


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