Endovascular Stroke Trials
Why We Must Enroll All Eligible Patients

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Is it appropriate to enroll into a clinical trial (and hence randomize to either medical or endovascular therapy) a 45-year-old patient who presents within 3 hours of onset of disabling symptoms resulting from a left M1 occlusion? This is the question many of us have faced in the course of the past few months because multiple new trials of endovascular stroke therapy have been launched on the heels of the neutral Interventional Management of Stroke (IMS)-III, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR-RESCUE), and Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) trials.1-3 The recently published IMS-III, MR-RESCUE, and SYNTHESIS trials have raised important questions related to efficacy of intra-arterial treatment. These trials have many flaws that have been eloquently discussed in some recent editorials and have raised interesting epistemological questions.4-6 Many neurologists, neurosurgeons, and interventional neuroradiologists have argued that randomization is unethical in such circumstances because patients like this one have the potential to do well with rapid recanalization but are likely to face a lifetime of disability without it. They support their argument by pointing out the poor natural history of the disease.4,5

In this article, we present a variety of perspectives on this question, reflecting the multiplicity of opinions within the stroke community. Ultimately, we think that these perspectives converge on the conclusion that we face a medical and ethical imperative to enroll our patients (even those who are young and with potentially devastating strokes) into clinical trials.

Standard of Care

Some critics of enrollment into endovascular stroke trials contend that endovascular therapy already amounts to the standard of care, and therefore, depriving patients of this treatment is negligent. Is this true? The standard of care may be established by:

1. Widely recognized robust clinical trial data: for example, level I evidence (eg, carotid endarterectomy for symptomatic carotid stenosis; backed by the North American Symptomatic Carotid Endarterectomy Trial [NASCET] and European Carotid Surgery Trial [ECST]).
2. The parachute scenario: the treatment effect is so large and well established historically that there is no possibility of an alternative (eg, antibiotics for meningitis).
3. A Grandfather clause: a particular technique has been practiced for a long time at many institutions with good outcomes and low complication rates in contrast to a bad natural history. No one has ever formally tested it, but overall, the belief is that the procedure is beneficial (eg, the treatment of dural arteriovenous fistulas that have cortical venous reflux).

Eventhoughtheprolyse in Acute Cerebral Thromboembolism (PROACT)-II trial showed a benefit for intra-arterial therapy, recent trials have shown us that the question being asked here is not backed by strong level I evidence.5 Furthermore, most experts would agree that the parachute scenario does not apply to intra-arterial therapy. Despite strong biological plausibility for the importance of recanalization, multiple clinical, physiological, and administrative factors (the clinical heterogeneity of stroke, the challenge of patient enrollment varying rates of
infarct progression, patient-specific collateral circulation, and the importance of good workflow) preclude establishing an obvious benefit for endovascular therapy at the present time. Recent clinical trials, endovascular complication rates, lack of overwhelming efficacy, and rapidly evolving changes to endovascular treatment also make it hard to convincingly invoke the Grandfather clause. Device and procedural complication rates from endovascular therapy remain significant (16% in IMS-III and MR-RESCUE).\textsuperscript{1,3} Patient outcomes without intra-arterial therapy are heterogeneous, with certain patients still doing well, particularly when intravenous tissue-type plasminogen activator (tPA) is administered. Endovascular stroke therapy is also not static but a rapidly moving target with transformation of technologies and techniques, both to achieve recanalization and to aid in image-based patient selection. The latest generation of devices, such as stentriever, has only recently been approved. Randomized controlled trials (RCTs) comparing stentriever with previously approved endovascular treatments have demonstrated improved safety but only modest improvements in efficacy.\textsuperscript{7,8} 

Arguably, the standard of care is established locally, and thus, an institution that has developed extensive experience in treating patients with stroke might argue that treating a 45-year-old patient straight to endovascular treatment is its standard of care. Is such a position justifiable? On the basis of available literature, we found that it is possible that some centers may be able to achieve good clinical outcomes routinely in a high proportion of carefully selected patients treated in an expedited fashion by highly skilled operators. To justify treatment standards from such local experience requires comparison with a historical control, which necessitates excellent long-term internal record keeping. Even with a high standard of record keeping, ascertainment bias in the absence of blinded assessments cannot be ruled out. Multiple studies have shown that operators think and even report that they are doing better than they really are, as recently reflected in the evaluation of the quality of recanalization by sites and the core laboratory in the Solitaire With the Intention for Thrombectomy (SWIFT) trial.\textsuperscript{9} In addition, there is the problem of recall bias: we tend to remember the good outcomes much more readily than the bad.\textsuperscript{10} Although our standard outcome measure for patients with acute stroke is the 90-day assessment, treating physicians tend to remember immediate results, and many stroke physicians may never follow-up with patients beyond the angi suite.

Moreover, leaving the decision of determining what is standard of care to the practitioners of a new therapy creates the potential for conflicts of interest. These may act at a subconscious or subliminal level. One possible conflict of interest is financial: under some medical systems, doing procedures may monetarily benefit physicians and hospitals, and this may alter practices either consciously or unconsciously. More subtle conflicts of interest may also affect treatment decisions: physicians like to do interventions and to try novel procedures that seek to build personal experience, endeavor to train the next generation, and have a genuine desire to advance the field. Although physicians are ultimately the source for what is standard of care, some checks and balances may be required to ensure that they are fairly engaging with experimental evidence, as well as their own experiences and beliefs.

**Equipoise**

Within the bioethics literature, the notion of equipoise is frequently cited to help resolve challenges around patient enrollment. Since its introduction in 1974, the concept of equipoise has been formulated in several different ways. As conceived by American lawyer Charles Fried, the original version of equipoise relates the ethics of clinical trial enrollment to a physician’s indecision about the 2 treatments being compared in the trial.\textsuperscript{11} It is only justifiable to enroll patients into a trial if the treating physician does not have a preference for one of those treatments. If the individual treating physician has a preference, for example, the physician thinks that endovascular therapy is superior to intravenous tPA for a left M1 occlusion, then that physician is ethically bound not to enroll the patient into a trial and is required to provide the patient with his or her preferred treatment. This position is referred to as the uncertainty principle in Europe.\textsuperscript{12}

This concept of equipoise is appealing to many physicians because it allows for the variability of individual decision-making and recognizes the complexities and particularities of specific patient presentations. At the same time, that variability is the weakness of Fried’s equipoise: every individual physician’s decision will be vulnerable to a long list of personal experiences, biases, and cultural factors. Moreover, it is rare for physicians to not have preferences about the treatment of any particular condition, which would make it difficult to ever enroll patients into trials. This scenario may be encountered frequently in acute stroke care.

A reformulation of equipoise was introduced in 1987 by Canadian bioethicist Benjamin Freedman.\textsuperscript{13} In this version, clinical trial enrollment is justified on the basis of the disagreement that exists within the medical community about the best treatment for a particular condition. Individual physicians are expected and allowed to have opinions that may differ, and those differences become the reason to enroll patients into trials. This version of equipoise is also referenced within the stroke community.\textsuperscript{14} However, Freedman’s conception of equipoise does not specify whose opinions should be counted, how much disagreement is required to justify a trial, or how we should establish what the opinions of a given community may be. For example, there exists a sense within at least part of the stroke community that endovascular therapy is superior to intravenous tPA. However, it becomes difficult to reject the conduct of clinical trials on this basis when there is no convincing trial data to support this opinion.

**Utilitarian Perspectives**

Utilitarian perspectives inform an alternative approach to the question of enrollment into endovascular stroke trials. Utilitarianism is a school of ethical thought that justifies decisions on the basis of amount of utility they produce; utility is defined in terms of the greatest good for the greatest number.\textsuperscript{15} A utilitarian approach to the issue of enrolling patients into endovascular stroke trials would consider irrelevant the opinions of particular physicians about what is best for individual patients. Rather, a utilitarian viewpoint admits that some patients will be harmed by being randomized to an inferior treatment (be it intravenous tPA or endovascular therapy), although conducting
trials and advancing medical knowledge will help more patients in the present and future. Utilitarianism also recognizes the importance of factors other than individual patient outcomes in the assessment of clinical trials. These include the responsibilities of government agencies to establish the efficacy of treatments to a certain standard of evidence (ie, the RCT).

Such utilitarian arguments would strongly support the enrollment of patients into clinical trials of endovascular stroke therapy and have gained support within the stroke community. However, the ethical and medical assumptions on which utilitarian perspectives are based will strike some clinicians as troubling. Utilitarianism requires us to calculate the utility produced by doing a trial; can we even do this if we don’t know what the results of the trial will be? Is clinical research so different from clinical practice that physician-researchers no longer have an obligation to ensure the best outcome for their individual patients? Would adopting utilitarianism harm the doctor–patient relationship that is central to the practice of medicine?

**Fallibility**

An emerging perspective on clinical research ethics arises from the recognition of physicians’ inherent fallibility. Fallibility is a notion adapted from the philosophy of science, which recognizes that human knowledge is never absolutely certain. Ultimately, any clinical opinion may be wrong; no matter how strongly a physician may think that endovascular therapy is beneficial for a 45-year-old patient with a left M1 occlusion, we cannot know what will be best for that patient or can we be certain that endovascular therapy is the best available treatment. All clinical opinions are constructed within, and necessarily affected by, a historical, political, and economic context. As a consequence, physicians must be open to reevaluating their practices, through clinical trials or other means. Multiple historical examples point to treatments that were considered the standard of care (for example, bloodletting for pneumonia or frontal lobotomy for depression) and that were ultimately proven to be ineffective or harmful. Incidentally, the originator of frontal lobotomy, Moniz, was awarded the Nobel Prize in 1949. Humility and skepticism are required to ensure that physicians are providing their patients with the best possible care based on the best available evidence. The enrollment of patients into endovascular stroke trials would be supported by a position built on the principle of fallibility.

**Pragmatic Considerations**

Practically, the approval of treatments (be they medicines or devices) occurs through complex mechanisms at the level of government agencies. Regulatory bodies like the Food and Drug Administration in the United States are charged with the responsibility of ensuring that a certain evidentiary bar has been met by any treatment before it is licensed for use. The National Institutes of Health and its equivalent institutions in Canada and Europe then provide the necessary infrastructure to help meet that bar. These institutions bear fiscal and social responsibility for their decisions: expensive and unnecessary treatments can be financially taxing for society, whereas good, useful treatments should be made available to all members of society.

These agencies, organizations, and institutions gain their authority and legitimacy from the support the public places in them through the democratic system. As a collective, these agencies have made it amply clear that RCTs constitute the bar that needs to be met before new treatments can be approved. Moreover, they have provided clinician-researchers with the financial and intellectual infrastructure to create and test new treatments and devices. Thus, from a practical standpoint, the question of enrolling a 45-year-old patient with a proximal vessel occlusion in a trial of endovascular therapy against intravenous tPA alone can be seen to have been answered by society (through its representative health agencies) rather than by the individual physician. By requiring RCTs for the approval of new treatments, society and its political institutions have already given their answer.

**Challenges of Conducting Trials**

As trialists, it is especially important for us to recognize that the results of the trials into which we enroll our patients are a summation of the results accrued from individual patients enrolled in the trial. It is possible that the effect of a given intervention (like endovascular therapy) is not equally distributed across the entire sample and that certain subgroups may disproportionately contribute to the final results. We assume that young patients with small infarct cores may be just such a subgroup that will demonstrate a large difference in outcomes between endovascular and intravenous therapy. Excluding these patients from trial enrollment may artificially skew the results of a large trial away from a beneficial therapy. It is for this reason that a poorly conducted RCT (that is, one in which a nonrepresentative, nonconsecutive sample of patients is enrolled), may potentially be worse than having no trial at all. It is also important to remember that we cannot reliably predict the differences in outcomes across various subpopulations of patients enrolled into any given trial; that is why we need trials in the first place.

We recognize that the design and conduct of clinical trials in contemporary medicine may introduce biases and conflicts of interest. Some researchers may be compelled not to enroll patients into certain trials that would promote competing therapies or research paradigms. Widespread recognition of the importance of consecutive clinical trial enrollment would draw attention to such conflicts of interest and potentially render them less palatable and less practicable. Alternatively, some centers or individuals may be compelled to pursue a particular research pathway, and thereby enroll patients into trials for personal or institutional financial gain. The fame/notoriety produced from a successful trial and high-impact journal publication can also be a huge motivation for the individual and institution that should not to be overlooked. Local review, research ethics boards, and funding agencies already have a mandate to screen for such issues, and perhaps they should do so more aggressively. Professional societies must be more engaged in the process of clinical trial enrollment, focusing the attention of an entire discipline on a particular question at a given point in time, to help advance the field. However, as one can imagine, this is a double-edged sword. Giving the societies too much power risks nepotism or even dropped membership
and people acting outside of it. Trials lose momentum with time and even relevance in some cases. A question should be studied with the full dedication of the field to complete the trial quickly with the best centers available. Once answered, the question is replaced by new question(s) and trial(s). Cardiology has advanced ST-segment–elevation myocardial infarction therapy in an efficient fashion with such an approach.

Other Considerations

Although we have been focused on the problem of randomizing patients to either intravenous tPA or endovascular therapy, the real-world translation of this issue raises a related question: is it justifiable to randomize a patient beyond 4.5 hours, or who has a contraindication to tPA (such as elevated international normalized ratio or recent surgery) to endovascular therapy versus standard stroke unit care? From a pragmatic point of view, there are 2 ways to look at this. On the surface, IMS-III and other similar trials have shown that endovascular treatment is equivalent to intravenous tPA. Intravenous tPA has been shown to be superior to nothing. Therefore, endovascular treatment is superior to nothing in patients who are not eligible for intravenous tPA. But digging deeper into this issue, there are flaws to that argument. Patients are generally not eligible for intravenous thrombolitics because they present too late for tPA, after which the risks of tPA outweigh the benefits (increased mortality >4.5 hours) or they have a contraindication to treatment, generally because the safety of tPA is questionable (high international normalized ratio, recent major surgery, subacute stroke, previous intracerebral hemorrhage).

We would argue that in such cases, there is little evidence that endovascular treatment is safer or even efficacious in such circumstances. In fact, the MR-RESCEUE trial illustrated the challenges of demonstrating a benefit from endovascular treatment when treatment is initiated >6 hours from symptom onset. Endovascular therapy may not be safe in subjects with high international normalized ratio readings because of increased hemorrhagic transformation and groin-related bleeding complications. Subacute stroke may also be associated with increased hemorrhagic transformation. Most important, if it is true that endovascular is equivalent to intravenous tPA and, therefore, better than nothing, are we able to convince the powers that be to state on a Solitaire or a Trevo package: approved for treatment of acute ischemic stroke presenting within 8 hours but having a contraindication for intravenous tPA? How would we do this? What would be the steps? What would the Food and Drug Administration (and other similar agencies) ask of us? We would be happy if this editorial is able to encourage policy makers and regulatory bodies to accept intra-arterial therapy as standard of care for such patients.

Trialists may struggle with 1 final, important question: should patients be offered a choice between intra-arterial therapy and enrollment in a clinical trial (in which they may or may not receive intra-arterial therapy)? This question strikes at the root of our position. If patients are offered endovascular therapy outside of a trial, then consecutive enrollment is compromised and bias is introduced into the trial sample. If we actually believe in clinical trial methodology (as a means of benefiting the most patients, as a defense against our own fallibility, or as our regulatory gold standard), then interventions that are being investigated in a trial should not be available outside of that trial. Although offering patients endovascular therapy outside of a clinical trial may seem to be in line with patient autonomy, our experience with such circumstances is that they force patients and their families to juggle multiple sets of statistics and protocols, producing confusion and delaying treatment, regardless of the decision made.

Conclusions

We have attempted to provide the reader with various perspectives on the complex issue of enrolling patients (especially young patients with proximal vessel occlusions) into endovascular stroke trials. When we, as physicians, are in the trenches faced with complex clinical scenarios, we make decisions on the basis of a combination of factors: knowledge, bias, belief, institutional policy, and experience. Results from recent trials have given us reason to doubt ourselves and to have the opportunity to learn from our mistakes. The need for more data from RCTs to further develop our practices is clear.

Let us now return to our original question: how should we manage a 45-year-old patient with a left M1 occlusion? Although we may think that this patient will do dramatically better with endovascular therapy than with medical treatment, we must be humble and recognize the fallibility of our opinions. Endovascular treatment is not yet the standard of care, and society holds us to a higher evidentiary standard than we have yet achieved. As British philosopher John Stuart Mill wrote 200 years ago, the greatest harm we can do to our own beliefs is to state on a Solitaire or a Trevo package: approved for treatment of acute ischemic stroke presenting within 8 hours but having a contraindication for intravenous tPA? How would we do this? What would be the steps? What would the Food and Drug Administration (and other similar agencies) ask of us? We would be happy if this editorial is able to encourage policy makers and regulatory bodies to accept intra-arterial therapy as standard of care for such patients.

Disclosures

Drs Goyal, Hill, and Demchuk are Principal Investigators for the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanulation Times (ESCAPE) study; Dr Menon is involved in design and conduct of the study. Drs Saver, Diener, Mendes, Levy, and Goyal are Principal Investigators for the Solitaire FR as Primary Treatment for Acute Ischemic Stroke (SWIFT PRIME) study. Drs Jovin and Davalos are Principal Investigators for the Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (REVASCAT) study. Drs Zaidat and Mocco are Principal Investigators for the Assess the Penumbra System in the Treatment of Acute Stroke (THERAPY) study.

References

Consecutive Enrollment in Stroke Trials


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