Ongoing Acute Endovascular Stroke Trials
Is Execution More Important Than Design?
Mayank Goyal, MD, FRCPC

With the failure of multiple recent acute stroke trials to show the benefit of endovascular treatment, there has been a lot written and spoken about next steps. In the wake of these results, many new trials have started with slightly varying principles, selection criteria, and depending on their sponsor, different devices. All these trials have tried to overcome the design limitations of the previously failed trials. However, there are certain general principles that we think we know well and essentially all ongoing trials are using these in the best way they think they can. What are these factors?

Dead Brain Is Dead Brain
It is clear that to be able to successfully demonstrate benefit of endovascular treatment, one has to choose patients with small core. Although there may be differences across trials, investigators, or the physician community at large about what is the best way of doing this, overall everyone agrees. It is also clear that there is a significant time interval between imaging and recanalization. As such, what may be more relevant to outcome is the amount of dead brain at the time of recanalization. In other words, if there was a way not only to measure dead brain on imaging but also to quantify the rate of progression of core to predict what the core would look like over the next 100 minutes or so when recanalization is achieved. This is currently unachievable.

Proximal vessel occlusions do not respond well to intravenous tissue-type plasminogen activator and are more suitable to endovascular thrombectomy (compared with distal occlusions). As such, all trials are aiming to choose only those patients with proximal vessel occlusion. Again there are slight variations in methodology. Most trials are using some form of noninvasive vascular imaging such as computed tomography angiography or magnetic resonance angiography; some trials are using the dense middle cerebral artery sign on the noncontrast computed tomographic scan. It is also well known that some patients with proximal vessel occlusion do respond to intravenous tissue-type plasminogen activator. However, we currently lack sufficient understanding of clot characteristics, clot size, flow parameters, etc., to reliably predict these patients.

Presence of Salvageable Tissue
Although there is general agreement in the concept of presence of penumbral or salvageable tissue for the patient to be part of the trial, there is lack of agreement regarding the definition of penumbra and the best way to quantify it. In a simplistic approach, some think that most patients early in their stroke will have some degree of penumbra; others are using clinical information such as a high National Institutes of Health Stroke Scale score (along with a small core) as an indicator for presence of penumbra. Other trials are using more imaging-based markers such as cerebral blood flow maps, $T_m$ maps (from perfusion imaging) or collateral assessment from single- or multiphase computed tomographic angiography. Irrespective, it is clear that patients who have no salvageable tissue are not suitable candidates for participation in a trial.

Time Is Brain
Based on multiple recent publications (from Intervventional Management of Stroke III [IMS3] and other nonrandomized data sets such as the Solitaire FR Thrombectomy for Acute Revascularization [STAR] study), we have now further confirmation of what we already knew: time is brain. This also means that to be able to show benefit of endovascular treatment, the recanalization in the endovascular arm has to be achieved within a short period from imaging (or even better from onset). Various trials are trying to accomplish in different ways. Some trials are attempting to accomplish an imaging (from computed tomographic head scan when one knows for sure that it is not a hemorrhagic stroke) to recanalization within 90 minutes. Others are aiming more toward an imaging to groin puncture time. The trials are using intensive training and quality control measures to achieve this and hopefully succeeding in this regard.

Adequate Sample Size
This is a more tricky one as here we are stuck with multiple constraints including budget (each patient enrolled costs significant monies; the budget for IMS3 for $35 million), availability of good centers that can demonstrate a good team, adequate imaging and workflow, and the infrastructure to conduct high-quality trials. There is also the issue of the total duration of trial, investigator tiredness, changing technology, and sustained funding.

Need for Good Quality Recanalization
The thrombolysis in cerebral infarction (TICI) scoring system is a well-established way to compare the quality of
recanalization across trials. Data from IMS3 and other studies have shown a clear correlation between the quality of recanalization and outcome. In IMS3, ≈40% of patients had a TICI 2B-3 flow.1 This has shown a dramatic increase with newer devices approaching 90% in some studies.9 In addition, we and others have noticed several patients in whom the final angiogram is better than a TICI 2B but not a TICI 3. We came up with the term TICI 2C.10 We have shown that there is a direct correlation with outcome as the quality of recanalization improves even from a TICI 2B to a TICI 2C.11 With the use of newer devices and better procedural training, we should aim to have a dramatic jump in high-quality recanalization compared with the older trials.

All this is now common knowledge. In fact, based on various data sets (including IMS3, STAR, and Calgary stroke program data sets), I have come up with an approximate value on the effect size between the 2 arms based on these factors (Table).

Why then can we fail? Or based on this and the design of the new trials, should we feel that these trials are just a formality? No. Because in my opinion, it is no longer about trial design, it is about trial execution. What are the key components of trial execution?

Choosing Good Centers

There are a limited number of good centers that have a well-established referral pattern, ability to perform sophisticated imaging fast, and then have a quick and accurate interpretation, having the necessary infrastructure and workflow to achieve efficient endovascular recanalization and finally the will to randomize patients. In the process of conducting these trials (I am one of the principal investigators of the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke [ESCAPE] trial and the Solitaire FR as Primary Treatment for Acute Ischemic Stroke [SWIFT PRIME] trial), I have had the opportunity to travel to >30 stroke centers. We are fortunate to be living in times that we have a large of centers that meet all these criteria; however, when one looks at the number of trials being done (or being planned) and all of them want to go to the same centers, suddenly the number starts to look small. In addition, some of the best centers have lack of willingness to randomize. I remember spending 3 hours with one of the best stroke centers (in my opinion) trying to convince the neurologists and interventionists of this center to randomize without success. Their logic was that their endovascular results are so good that they cannot ethically randomize patients.

Education and Quality Assurance

This is key especially in the domains of imaging-based selection and achieving excellent workflow and fast recanalization. Not only does this require tremendous effort from the trial leaders, but also requires willingness on the part of centers for change. Overall, no one likes change especially when the change involves moving dramatically faster, introducing the possibility of driving to the hospital at 2:00 AM on a snowy night and finding out the patient got randomized to the control arm. It is important to recognize that not one solution fits all hospitals. As such, I strongly think that the process of education has to be a 2-way street: understanding the strengths and weaknesses of each site and helping them achieve their best. Also, it is more than likely that there are going to be

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<th>Table. Approximate Effect Size Based on Modeling of Data From IMS3, STAR Study, and Calgary Data</th>
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<td><strong>Problem</strong></td>
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<td>Workflow</td>
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<td>Quality of recanalization</td>
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<td>Some patients with large core enrolled</td>
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<tr>
<td>Not all patients had a proximal vessel occlusion</td>
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Approximate effect size based on modeling of data from IMS3, STAR study, and Calgary data in newer trials (using ESCAPE and SWIFT PRIME as examples) compared with the older trials (using IMS3 as an example).1,6,8,11 Of note, it is also likely that the control arm in the newer trials may do worse than the previous trials because of (1) intravenous tissue-type plasminogen activator being given ≤4.5 hours and (2) all patients have known proximal vessel occlusion. ASPECTS indicates Alberta Stroke Program Early CT score; CT, computed tomography; CTA, computed tomography angiography; ESCAPE, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; ICA, internal carotid artery; IMS3, Interventional Management of Stroke III; MRA, magnetic resonance angiography; mRS, modified Rankin scale; STAR, Solitaire FR Thrombectomy for Acute Revascularization; SWIFT PRIME, Solitaire FR as Primary Treatment for Acute Ischemic Stroke; and TICI, thrombolysis in cerebral infarction.
other centers that are also facing similar issues. One way is to have increased interaction across sites and rather than having the education and quality assurance as a top-down initiative, think of it more like cross-pollination of ideas and practices. In addition, it would be important to predefined measurement and clear mandate to the consequences of poor performance. As an example, I was recently faced with an issue of a center that enrolled 2 consecutive patients in whom there was no demonstrable occlusion on the computed tomography angiography done before randomization. Although this of course is an obvious trigger for further education on imaging, trial criteria, it also requires a better understanding of the workforce within that center and if it is determined that the problem is nonsolvable, then to recognize it early and excuse the center from the trial.

Consecutive Enrollment
I have previously written on this topic. This, in my opinion, is the single biggest challenge that we currently face. It is not easy to randomize a 50-year-old otherwise healthy patient, 2 hours from onset, National Institutes of Health Stroke Scale core of 17, M1 occlusion, and a small core to a trial especially, when one practices in a good stroke center with extensive experience and success with endovascular thrombectomy. However, as I have previously written, it is important to recognize the following: (1) Trial results are a summation of all the data in the trial. It is possible and likely that the effect size of endovascular treatment is not evenly distributed across the entire data set. Selectively enrolling patients means potential reduction in effect size (meaning an exponential increase in sample size to demonstrate the effect) and of course, slower enrollment. (2) Endovascular treatment of stroke is not the standard of care. In fact, in view of the recent negative trials, one cannot apply the parachute analogy and claim that it should be exempt from randomized controlled trials in view of bad natural history of disease and dramatic effect size. The only way to continue to offer endovascular therapy for acute stroke is by showing positive randomized controlled trials.

Overcoming Delays in Getting Centers Up and Going
There is wide variability in the amount of time it takes to get a center up and going ready to randomize. The key components are Institutional Review Board approval of the protocol, a contract with the hospital, and training of the participants. In addition, some trials may have additional requirements such as installation of additional software. Managing these local variables is best done by the site principal investigator and, of course, by planning for all these events. However, in my experience, the single biggest factor to overcome delays is presence of a local champion who is in the best position to understand the processes and move things along.

Hold the Line
Trialists may have a tendency to panic if a few unexpected bad events happen especially in the treatment arm. As such, there may be a tendency toward multiple protocol amendments. This has the potential to introduce confusion among the investigators and, of course, deployment of scarce resources toward the amendment and all the necessary work that goes along with it such as training, resubmission to Institutional Review Boards. If one concurs with the central theme of this editorial, it is not about trial design; it is more about trial execution, then one would agree that it is important to hold the line. The commonest cause for a few unexpected bad events is randomness. Of course, it should trigger investigation and education.

Managing Changing Expectations, Technology, and Referral Patterns
Technology in acute stroke endovascular therapy has been changing at a rapid pace. There is no reason to think that is going to stop. When a major change in technology happens during a trial, it raises a few different problems. (1) The new technology may be attractive, but ultimately its efficacy and safety may be unknown. How this should be accounted for in the trial. (2) There may be a mass movement toward the new technology, and if it cannot be used within the trial (because of lack of safety data or just because it is going through the necessary paperwork through various amendments), it may lead to decreased enrollment because investigators may not want to enroll patients in the absence of the option of using the new technology. (3) Many of the newer trials are industry sponsored. If the new technology belongs to a competitor, it could potentially affect the funding for the trial. What are the solutions to these issues? The most obvious one of course is to have fast enrollment and complete the trial in a short period of time before there are major changes in technology. The other one is having greater cooperation among industry and discussion and negotiation with organizations such as Food and Drug Administration to consider a class approval for endovascular devices rather than individual devices.

In addition, there is the issue of referral patterns. A drip and ship paradigm clearly induces delays that selectively affect the endovascular arm of the trial. In addition, there are other potential problems associated with patients not coming directly to the hospital participating in the trial. I recently visited an excellent stroke center where most of their patients are referred in from smaller hospitals. There are 2 hospitals not too far from each other. One hospital (the one I visited) believes in trials and evidence-based medicine, whereas the other does not. As soon as the trial starts, the hospital that is not part of the trial actively markets its absence of trial and randomization to the referring hospitals to capture the market. This is not easily solvable in the short term. Hopefully, it is a relatively rare occurrence. In the long term though, the solution lies in creating a culture of evidence-based medicine that starts at the medical school level.

In conclusion, I do think that we have learnt from all the years of hard work and failed trials. I do think we know the key design components to demonstrate the superiority of endovascular treatment in a select population of acute ischemic stroke. I agree that there is significant controversy and variability across ongoing trials regarding how these key design components are implemented. However, a well-designed, poorly executed trial can still fail. Successful trials
are going to require hard work, leadership and cooperation of all stakeholders including hospitals, referring doctors, professional organizations (Society of Neurointerventional Surgery, American Heart Association, etc), and a commitment to trials and evidence-based medicine.

Disclosures
Dr Goyal serves as consultant for Covidien-ev3 and as co-principal investigator for ESCAPE and SWIFT PRIME trials.

References

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