Challenges of Acute Endovascular Stroke Trials

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Intravenous thrombolytic therapy with tissue-type plasminogen activator (tPA) has been approved for acute ischemic stroke since 1996. However, its tight time window means that many centers only treat a minority of patients. Effectiveness is limited by the low recanalization rates of large intracranial occlusions (4% distal internal carotid and basilar artery and 32%–37% M1 middle cerebral artery), which has high disability and mortality. Clinical outcome at 3 months is strongly associated with the timeliness and extent of reperfusion. These findings call for therapies beyond intravenous tPA to improve clinical outcomes in such patients.

There is an unmet need to develop efficient therapies for acute stroke caused by proximal intracranial occlusion. Three recent endovascular randomized controlled trials (RCTs) were negative. These trials have been criticized for the use of older first-generation devices, slow recruitment, delayed times to reperfusion, and nonuniform requirement for demonstration of large-vessel occlusion for enrollment. Second-generation devices (Solitaire, Trevo), now referred to as stentriever, in 2 RCTs have shown improved outcomes over the first-generation Merci device.

Despite the absence of phase III randomized controlled trials showing their superiority, there has been a 6-fold increase in the endovascular procedures in the United States between 2004 and 2009 (0.1%–0.6%) when compared with a tripling in usage of intravenous tPA (1.2%–3.4%). This increase likely represents changes in the systems of developing treatment pathways for acute stroke victims.

It is clear that further clinical trials are needed to provide definitive evidence that endovascular therapy is an effective adjunct to intravenous tPA. Several new trials have been started. Although there is hope that this generation of trials will show the superiority of endovascular treatment, it is important to recognize the challenges that these trials face. In addition, given the multiplicity of trials and limited number of large volume stroke centers with endovascular capabilities and potentially limited number of patients meeting the selection criteria, it is likely that enrollment in these trials may be slower than expected. As such, what is perceived to be the greatest challenges facing these randomized trials are presented here.

Challenges

Endovascular Procedure

Fast-Moving Field; Changing Technology

The specialty of Neurointerventional Surgery is evolving. The release of the Merci device in 2005 established the obvious attraction of a thrombectomy device that could remove clot. However, the device was limited by modest recanalization rates. Similar findings were described with the earlier versions of the Penumbra aspiration system. More recently, stentriever have been shown to improve the ability to revascularize...
occluded vessels significantly better than the Merci device, but with a moderate additional degree of improvement in the functional outcome. Stentriever devices were used in few patients in the recent neutral RCTs of endovascular therapy. Moreover, the enthusiasm for new technology needs to be balanced against the lack of experience supporting their safety.

Novel methods for mechanical thrombectomy continue to emerge. Trackable large bore aspiration catheters were recently released and markedly expedite the time and ability to perform aspiration of occluded vessels. Reports combining these technologies and approaches have shown promising results, with successful recanalization in nearly all cases.

This rapid evolution of both technology and technique is expected to pose a challenge in the choice of devices for endovascular trials. One solution is to add new devices through protocol amendments, a lengthy process that may take months. During that time, certain centers may refrain from enrolling patients into the trial because they have completely adopted the new device/technology. Alternatively, trial protocols may choose to be inclusive and allow any approved device that operators believe to yield the best results. This approach assumes equivalence of different devices in safety and effectiveness and absence of a learning curve across devices. The answer to this is also influenced by organizations, such as US Food and Drug Administration, that require a device-specific protocol amendments, a lengthy process that may take months.

Delays in the Endovascular Arm

Delays in delivery of endovascular therapy are inevitable. There are established timelines to regulate intravenous tPA administration, which can be started in the computed tomographic (CT) scanner. In endovascular therapy, delays occur during screening, randomization, informed consent, travel of the interventional team, and during the procedure itself. In the Interventional Management of Stroke-III trial, the median time from intravenous tPA bolus to groin puncture was 85 minutes, whereas the median time from start of intravenous tPA to randomization was 24 minutes. With a groin puncture to successful reperfusion median time of 34 minutes in the Solitaire FR Thrombectomy for Acute Revascularisation (STAR) study, a potential delay of ≈2 hours exists from intravenous tPA initiation to successful endovascular reperfusion. For endovascular trials to compare the treatment effect to intravenous tPA, delays that preferentially affect the endovascular arm should be minimized. The process of reducing delays is dependent on infrastructure, available personnel and support services, and sufficient patient volume. Delays are potentially worse in the setting of RCTs, which require informed consent, checking for inclusion and exclusion criteria, and randomization. In addition, lower volume endovascular centers have lengthier times to reperfusion when compared with centers that perform >50 endovascular stroke cases annually. These high volume centers have well-established workflows that shorten treatment times as the endovascular gets activated for potential trial candidates at the risk of a 50% chance of the subject being enrolled into the control arm. Some people are of the opinion that in situations such as T occlusions where the likelihood of recanalization with intravenous tPA is low, the intravenous tPA may be bypassed and that these patients be taken straight for the endovascular procedure. These could reduce some delays. However, this approach does not have widespread acceptance for a variety of reasons. Although the likelihood of reperfusion with intravenous tPA in major occlusions is relatively small, it is not negligible. Also, there could be insurmountable challenges during the endovascular procedure: peripheral vascular disease, abdominal aortic aneurysm, tortuosity, patient cooperation, etc. As such, there is always a possibility of not reaching the clot in a timely fashion during an endovascular procedure. Finally, there is also the issue of standard of care. Although many think that intravenous tPA has little effect on major occlusions as T occlusion, the current guidelines do not address that.

Consent

In the RCT setting, the consent process only affects the endovascular arm because the control arm can receive appropriate treatment as standard of care before trial consent. Although various strategies have been discussed and some of them are being tried (eg, deferral of consent in most centers in the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times [ESCAPE] trial), the current standard for most IRBs is consent from a surrogate decision maker. Because of the time-sensitivity of stroke treatment, this leads to delays in the intervention and exclusion of patients when no surrogate decision maker is available. Discussion among the stroke community is needed about evolving to trial designs where waiver or deferral of informed consent is possible.

Referral Patterns, Drip and Ship Versus Mother Ship

There are significant issues related to referral patterns in acute stroke trials. Most importantly, the absence of a defined regionalized referral system makes both acute stroke care and trial enrollment challenging. Currently, only a small fraction of patients having ischemic stroke receive intravenous tPA. The percentage of patients who are candidates for endovascular intervention, and the numbers who actually receive such therapies, are not easily estimated. This subgroup may represent ≈22,000 patients per year in the United States. An exception to this phenomenon are community hospitals that initiate intravenous tPA and then transfer to stroke centers with capabilities (drip and ship) for potential endovascular treatment. The increasing frequency of drip and ship referrals led to previous and ongoing RCTs allowing enrollment of such patients. However, in a detailed workflow analysis of the Interventional Management of Stroke-III data, there was a clear delay introduced by the drip and ship paradigm when compared with the mother ship. In addition, many have described worse functional outcome in the endovascular population of transferred patients.

Variation in Operator Training and Experience

Many questions relating to this issue remain unanswered. These include questions relating to what constitutes a well-trained interventionalist and how can that be measured or standardized. Whether the answer to these queries should be based on experience (eg, having treated 50 stroke cases) or on outcomes (eg, having 50 strokes treated with low intra-procedural complications) requires consensus among the
endovascular community. Moreover, whether experience in other endovascular areas, eg, coiling aneurysms or embolizing brain arteriovenous malformations, would count toward experience in treating stroke is hard to resolve. Finally, issues relating to center selection and whether the overall systems efficiency can be a major criterion for selection remain to be addressed. One potential methodology is for centers to demonstrate efficient (<90 minutes from CT head) and high-quality (Thrombolysis in Cerebral Infarction 2b or higher) recanalization in ≥5 patients.

The pharmacological treatment of acute stroke is performed in the same way worldwide, whereas an endovascular procedure is not standardized and operator dependent. Among the difficult questions in this area include whether it is possible/advisable to define the endovascular treatment in a trial and defining procedures or devices that would constitute a protocol deviation or violation. The adoption of checklists that are already in use in different surgical disciplines, to reduce complications, has not been addressed by the endovascular regulatory bodies. In this regard, the role that professional societies should play versus the interventional community about training, procedure, devices, etc. is yet to be defined.

**Use of General Anesthesia**

General anesthesia has been associated with worse functional outcomes and intensive care unit–related complication, such as pneumonia or sepsis, in several cohort studies. To avoid these potential detrimental effects, one solution is for endovascular trials to discourage the routine use of general anesthesia in participating centers. Furthermore, the presence of a physician with critical care training (neurointensivist and anesthesiologist) to manage the conscious patients, while the interventionalist performs the procedure, would be desirable but has its challenges.

**Standardization of the Endovascular Procedure and Associated Issues**

1. The endovascular procedure: from a practical aspect, there are 2 main concerns: (1) different devices or techniques may have varying complication and efficacy rates. Merging different devices has the potential to affect the endovascular arm in unpredictable ways. (2) In addition, it is unclear whether the technique of endovascular procedures should be precisely specified (eg, the use of a balloon guide catheter and suction during stent-retriever retrieval).

2. Approval of device: the US Food and Drug Administration (and other similar organizations) requires precise protocols within the endovascular arm, a precise definition of technique and usage of a single device, to grant approval of the device for stroke treatment. This means that studies may have to limit the devices used and standardize techniques for obtaining approval.

**Imaging-Based Patient Selection**

Most centers agree that the use of noninvasive CT or MR angiography to confirm the presence of a target vessel occlusion and to assess proximal vascular access is a prerequisite for endovascular patient selection. Previous trials did not mandate such imaging, leading to a substantial proportion of patients without a clearly defined treatable lesion. CT/MR angiography is now readily available in all centers capable of endovascular therapy. Some trials are using the dense middle cerebral artery sign on noncontrast CT as a marker for proximal vessel occlusion.

The degree to which further patient selection is required remains a contentious topic. Brain tissue beyond an occlusion is dependent on collaterals for survival until the clot is lysed and sufficient anterograde perfusion is achieved. Therefore, it is intuitive to assume that patients with poor collaterals at baseline will have large ischemic cores and consequent poor clinical outcomes even with rapid and complete reperfusion. The key issue to be addressed is whether efforts should be made to exclude such patients from endovascular trials. This decision depends on the prevalence of patients with baseline poor collaterals, the degree of risk posed to them by reperfusion, whether some differential benefit may still be achieved by reperfusion (even if they do not reach modified Rankin Scale, 0–2), and the potential delay to reperfusion incurred using imaging techniques to identify these patients.

Data indicate that 10% to 20% of patients presenting with major vessel occlusion have large ischemic core or poor collaterals. These patients could potentially benefit from early reperfusion but are unlikely to achieve functional independence. Trial outcome measures have traditionally struggled to account for shifts from severe to moderate disability that clinicians still regard as valuable. Ordinal analysis of the modified Rankin Scale could capture a differential response to intracerebral therapy; nonetheless, this is 1 group of patients where current literature suggests least likelihood of eliciting such a differential response.

Imaging modalities capable of identifying large ischemic core include noncontrast CT Alberta Stroke Program Early CT score (ASPECTS), CT angiographic collaterals (including static and multiphase acquisitions), CT perfusion (thrombolysed cerebral blood volume or cerebral blood flow) and diffusion MRI. The choice among these modalities has to take into consideration the acquisition and interpretation times, precision, and inter-rater agreement. The noncontrast CT ASPECTS is universally available but is less reliable, particularly early after stroke onset. Poor collateral flow on CT angiography is a good surrogate for large ischemic core, a multiphase acquisition with this modality corrects for mislabeling of collateral status with single phase CTA (because of variability in bolus timing and scanner speed). This technique is rapid, significantly more reliable than noncontrast CT and does not need postprocessing algorithms. CT perfusion also acquires blood flow images temporally, such as multiphase CTA acquisitions, and can be automated to provide detailed spatial and volumetric information on blood flow rapidly. CTASPECTS. Trialists need to achieve an optimal balance among sensitivity, reliability, speed of acquisition, and interpretation for each of these modalities that gives endovascular trials the best opportunity to show differential response with intraarterial therapy. The most robust determinant of good clinical outcome that we know of is early reperfusion. Achieving faster reperfusion while selecting appropriate patients should
be the goal for all endovascular trials. Of note, although diffusion MRI can be acquired in <2 minutes, unfortunately in most centers MRI access and safety procedures introduce substantial delays to reperfusion.

In the current endovascular research landscape, the existing body of neutral trials provides a strong motivation to improve the chances of success in ongoing trials. Excluding patients with a large ischemic core, therefore, seems a logical approach if achieved without causing delay in achieving reperfusion. Current clinical trials use varying approaches to patient selection; however, the goal should be to use an imaging technique that is reasonably accurate, reliable, widely available, and does not cause any delay to workflow. It is this philosophy that will give our community the best chance to see a positive endovascular trial.

Trial Design and Conduct Challenges

Sample Size, Resources, and Finishing the Trial: Practical Considerations

The statistical design of a trial is scientifically determined by an explicit articulation of the clinical question and the minimal clinically important difference. Practical considerations on what is reliably measureable and what is the immediate medical-sosocial environment make clinical trial design an art. Stroke is such a devastating condition that even a small difference in outcomes could be meaningful on a population basis. However, endovascular therapy applies to <10% of all ischemic strokes; requires a dedicated, highly trained team; requires specialized technical equipment and is expensive to perform well. These considerations mean that a moderate to large effect size must be demonstrated to justify the investment in the team, equipment, and stroke care organization to improve care.

It is now possible to achieve near-perfect angiographic results in ≥80% of acute stroke interventions. Nonetheless, reperfusion may not stop the progression to infarction if bioenergetic failure is too advanced; choosing patients with salvageable tissue is critical. Also, incomplete rehabilitation or comorbid illness could result in a poor outcome, despite good angiographic results. Variability in patient care by center or health system over the ensuing 89 days after the procedure also likely contributes to variance in outcome but in stroke is probably dwarfed in magnitude by the disease itself. These factors mean that there is a ceiling on the good outcome rate that is often underappreciated. This issue is especially important to ensure adequate sample size calculations for the trial.

The use of clinical outcomes has been the standard in recent major stroke trials. These mostly used functional outcomes assessed at the 90-day mark via the modified Rankin Scale score dichotomized to indicate favorable outcome for scores of ≤2. Recent work has supported the concept that the modified Rankin Scale is a monotonic scale on a clinical basis, except for similarity of value of the 2 most severe levels, 5 and 6, which supports the use of the proportional odds model to assess change across all remaining 6 levels of the scale. The shift analysis does not necessarily result in greater power to detect a treatment effect; power will depend on the distribution of scores in each arm of a trial. Nonetheless, the use of shift analysis is more likely to capture relevant differences in modified Rankin Score distribution across the 2 arms of a study than a prespecified threshold.

Consecutive Enrollment Monitoring and Generalizability of the Trial

Internal validity of a trial is limited when a substantial number of eligible patients are presumably treated outside of the trial. Eligibility based on the uncertainty of the most appropriate choice introduces an important bias and may dilute potential beneficial effects. 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. Excluding these patients from trial enrollment may skew the results of a large trial away from a beneficial therapy artificially.

Future trials must implement mechanisms to minimize selection bias and to capture eligible patients treated outside of the trial. A helpful choice is using government-mandated and government-audited population-based databases of reperfusion therapies for acute ischemic stroke, including endovascular therapies. These registries enable determination of compliance on the part of the treating centers with their commitment to enroll all eligible patients and ensure minimization of selection bias. In addition, such registries will improve the hyperacute stroke workflow in participating centers in preparation for participation in future RCTs. Continuous feedback on patients treated outside the trial allows the possibility of implementing corrective actions in case of noncompliance.

Funding Issues

The acute endovascular stroke trials during the past decade have highlighted some important issues on funding because it pertains to clinical trials. One ongoing debate is whether mechanical thrombectomy should be reimbursed outside of the context of randomized controlled trials. Currently, thrombectomy is reimbursed by Centers for Medicare and Medicaid Services outside of clinical trials even though there remains no class I evidence supporting its use. Whether this is truly an impediment to scientific progress in the context of trial performance or actually facilitates appropriate infrastructure development to allow successful trial performance remains unsubstantiated.

During the past decade, there has been a shift from National Institutes of Health–supported funding toward private funding from industry. The main impetus for this shift has been the difficulties in obtaining and maintaining National Institutes of Health funding in the setting of governmental budget cuts. Today, nearly all active thrombectomy trials are funded by private industry. Although easier to obtain, private funding imparts specific challenges. Most notably, private funding often mandates the use of specific devices, which may limit the investigator’s ability to design the study for the purpose of demonstrating benefit from thrombectomy in stroke, as opposed to demonstrating efficacy for an individual device in that setting.

Implications of Positive Trial Results

Positive randomized trial results demonstrating that final patient outcome is improved by neurothrombectomy
interventions would have transformative effect on stroke care. It would lead to profound changes in organizing regional acute stroke care to ensure delivery of appropriate patients to neuroendovascular centers, similar to the transformation that took place in regional organization of acute cardiac care after positive results from acute coronary angioplasty trials. With definitive randomized controlled trial data available to drive system change, support of hospital executives, payors, and emergency medical services (EMS) leaders would be elicited to implement 2-tier systems of care incorporating Comprehensive as well as Primary Stroke Centers. Patient triage and routing considerations would add destination hospital neuroendovascular capability to the current elements of availability of intravenous tPA and organized stroke unit care, transport distances, and patient preference. Policies would permit direct ambulance routing to an endovascular center for patients who are beyond the time window for intravenous tPA but within the window for neurothrombectomy. Depending on the degree of added benefit of neurothrombectomy above that of intravenous thrombolysis, policies could also permit direct ambulance routing to an endovascular center for patients whose stroke severity scores or deficit patterns indicate they are likely harboring proximal large-vessel occlusions that may distinctively benefit from neurothrombectomy.

In the wake of positive trials, attention within neurothrombectomy centers would turn toward implementing continuous quality improvement programs to optimize daily practice. Given the critical importance of time to outcome from neurothrombectomy, intensive efforts to accelerate treatment would be undertaken, focusing on door to groin puncture, door to microcatheter on clot, door to reperfusion, and related metrics. With the multiple endovascular trials that are currently enrolling patients, the enthusiasm to enroll patients may dampen if one trial emerged positive, whereas the rest are still enrolling. The ethical and clinical implications of a positive trial may be hard to anticipate but could potentially lead to the early stoppage of some enrolling trials. Similarly, a negative trial may further reduce the enthusiasm of centers or funding agencies in supporting future trials. Early planning of pooling data from current and future trials for patient-level meta-analyses may become a necessity in anticipation of these circumstances.

**Implications of a Negative Trial Results**

Additional negative trial results carry the risk of halting progress in the field of endovascular treatment of acute stroke. Doctors, administrators, and industry found a way to move forward at the end of the previous series of negative trials given changes in endovascular technology, better imaging, improved workflow, and an overall better understanding of the factors responsible for potential failure of the previous trials. Current ongoing trials will carry an expectation of having solved many of the problems of the previous trials with them. Although there will always be additional problems to solve, another negative trial using modern technologies may not be looked on kindly by the community. Randomized controlled trials carry weight especially for policy decision, funding, and innovation. This should be kept in mind as we move forward. Although there are many potential reasons as outlined in this article for failure to show the benefit of endovascular treatment, with properly chosen centers, commitment to consecutive enrolment, teamwork, cooperation, and leadership, these can be overcome.

**Suggested Specific Solutions**

Here, we attempt to provide some specific solutions to the challenges listed above. These are not meant to be a comprehensive list to solve all problems but could serve as a starting point.

1. Food and Drug Administration to agree to class approval for similar devices that have similar data from current published literature. This, in our opinion, would go a long way toward solving many of these problems. First, it would encourage companies to work together rather than competitively to get the trial done. Second, procuring funding for trials would be easier. Third, similarly designed trials would not compete with each other to get the best centers to participate in their trial.

2. Professional societies and opinion leaders to come up with specific guidelines related to workflow and efficiency. As an example, if there was general consensus that the total amount of time that could be devoted to imaging (including post processing and decision making) could not exceed 10 minutes, it would force all trialists to make similar judgment calls related to imaging protocols. In addition, it would also encourage innovation from imaging vendors. Similar guidelines related to procedure time would force creation of better training facilities and module and improve standardization of the procedure across centers. Once again, it would encourage innovation in various domains, including virtual simulation angiography, thrombectomy, etc.

3. Given that the particularities of acute stroke (urgency, complexity, and variability) make waiver of consent an option that the particularities of acute stroke (urgency, complexity, and variability) make waiver of consent an appropriate enrollment mechanism, trial investigators and sponsors should implement it more often in conjunction with ethicists, regulatory authorities, and institutional review boards. Wider use of exception from informed consent would not only save time but also increase enrollment substantially.

**Conclusions**

In the wake of failure of recent endovascular trials to demonstrate the benefit of endovascular treatment, there is a clear need for additional trials. Many new trials have been started, with some variations in inclusion/exclusion criteria and endovascular technique/device usage. It is important to understand the challenges that these current and future trials face. These include issues related to patient selection, sample size, referral pattern, consecutive enrollment, funding, individual device versus class approval, training, and the implications of delays that affects only the endovascular arm. We have presented a description of these challenges from personal experiences in previous and ongoing trials. Although we have attempted to present some potential solutions, our hope is to encourage further discussion among all stakeholders and to increase the collaboration across trials and industry.
Disclosures

Dr Goyal has a consultant or advisory relationship from Covidien ev3 (Significant; >$10K or 5%). Dr Broderick received modest honoraria (<$10K or <5%) from Covidien for Courses-teaching and from Neuravi as Speaking fees. He serves as a proctor for Stryker (modest; <$10K or <5%), and as a consultant for Neuravi and Rapid Medical (both modest; <$10K or <5%). Dr Broderick received research grant (Significant; >$10K or 5%) from the National Institute of Neurological Disorders and Stroke (NINDS) as the PI for the Interventional Management of Stroke (IMS) III trial, and research support (Significant; >$10K or 5%) from Genentech for steering committee for A Study of the Efficacy and Safety of Activa (Allotplace) in Patients With Mild Stroke (PRISMS) trial and study medication for IMS III Trial. Dr Demchuk received unrestricted research grant from Covidien for Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanlization Times (ESCAPE) trial (no compensation) and honoraria (speaker fees for CME events) from Covidien (modest; <$10K or <5%). Dr Gupta serves as a consultant for Stryker, Covidien and Rapid Medical (all modest; <$10K or <5%). Dr Jovin serves as a consultant for Silk Road Medical (modest; <$10K or <5%). Pooja Khatri received research grant to her department from Genentech for role as PRISMS trial PI (significant; >$10K or 5%) and from Penumbra as Assess the Penumbra System in the Treatment of Acute Stroke (THERAPY) trial Neuro PI (Significant; >$10K or 5%). Dr Murphy is an advisory board member to Daichi Sanyo and to Boehringer-Ingelheim (both modest; <$10K or <5%). Dr Nogueira received compensations from Stryker Neurovascular as PI for Thrombectomy REvascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO)-2 and Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes (DAWN) trials (modest; <$10K or <5%), and from Covidien for serving as Steering Committee for Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT) and SWIFT Prime Trials; Core Lab for Solitaire FR Thrombectomy for Acute Revascularisation (STAR) trial (Significant; >$10K or 5%). He serves on the Executive Committee for Penumbra 3D Separator Trial (no compensation). Dr Siddiqui received research grant (Significant; >$10K or 5%) from the National Institutes of Health as co-investigator for (1) NINDS 1R01NS064592-01A1, Hemodynamic induction of pathologic remodeling leading to intracranial aneurysms; and (2) National Institute of Biomedical Imaging and Bioengineering (NIBIB) 5 R01 EB00873-07, Micro-Radiographic Image for Neurovascular Interventions. He was the recipient of the Research Development Award from the University of Buffalo (Modest; <$10K or <5%). He received modes compensation (<$10K or <5%) for speakers Bureau membership from Codman & Shurtleff, Inc. He also received compensations for training from Penumbra, Inc. (modest; <$10K or <5%) and from Abbott Vascular (modest; <$10K or <5%). He reports financial interest in Hotspur (Significant; >$10K or 5%), Intratech Medical (Significant; >$10K or 5%), StimSox (Moderest; <$10K or <5%), Valor Medical (Significant; >$10K or 5%), Blockade Medical (Moderest; <$10K or <5%), Lazarus Effect (Moderest; <$10K or <5%), and Pulsar Vascular (Moderest; <$10K or <5%). He received consultancy compensations from: Concentric Medical (Moderest; <$10K or <5%), GuidePoint Global Consulting (Moderest; <$10K or <5%), Penumbra (Moderest; <$10K or <5%), Stryker (Moderest; <$10K or <5%), Lazarus Effect (Moderest; <$10K or <5%), and Blockade Medical (Moderest; <$10K or <5%). He received compensations for serving as Consultant and Advisory Board member from Codman & Shurtleff, Inc. (Significant; >$10K or 5%), and from Covidien Vascular (Significant; >$10K or 5%). Dr Turk III received research grants from Microvention (Significant; >$10K or 5%), Penumbra (Significant; >$10K or 5%), Siemens (Moderest; <$10K or <5%), and Covidien (Moderest; <$10K or <5%). He received presentation honoraria from Microvention (Moderest; <$10K or <5%), Penumbra (Moderest; <$10K or <5%), Siemens (Moderest; <$10K or <5%), Covidien (Moderest; <$10K or <5%), and Medpace (Moderest; <$10K or <5%). Dr Saver: The University of California, Regents receive funding for Dr Saver’s services as a scientific consultant regarding trial design and conduct to Covidien, CoAxia, Stryker, BrainsGate, Genervon, St. Jude Medical, and Grifols. Dr Saver has served as an unpaid site investigator in multicenter trials run by Lundbeck and Covidien for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled. The University of California has patent rights in retrieval devices for stroke. The authors also report no conflicts.

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