Stroke

SPECIAL REPORT

How to Establish the Outer Limits of Reperfusion Therapy

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ABSTRACT: Reperfusion therapy with intravenous alteplase and endovascular therapy are effective treatments for selected patients with acute ischemic stroke. Guidelines for treatment are based upon randomized trials demonstrating substantial treatment effects for highly selected patients based on time from stroke onset and imaging features. However, patients beyond the current established guidelines might benefit with lesser but still clinically significant treatment effects. The STAIR (Stroke Treatment Academic Industry Roundtable) XI meeting convened a workgroup to consider the "outer limits" of reperfusion therapy by defining the current boundaries, and exploring optimal parameters and methodology for determining the outer limits. In addition to statistical significance, the minimum clinically important difference should be considered in exploring the limits of reperfusion therapy. Societal factors and quality of life considerations should be incorporated into assessment of treatment efficacy. The threshold for perception of benefit in the medical community may differ from that necessary for the Food and Drug Administration approval. Data from alternative sources such as platform trials, registries and large pragmatic trials should supplement randomized controlled trials to improve generalizability to routine clinical practice. Further interactions between industry and academic centers should be encouraged.

Key Words: ischemic stroke ■ magnetic resonance imaging ■ reperfusion ■ thrombolysis ■ tomography

Since the publication of the landmark trials in 2015 and 2018, endovascular therapy (EVT) has become standard treatment for ischemic stroke related to large vessel occlusion up to 24 hours after onset. Intravenous thrombolysis (IVT) is an established therapy worldwide for selected patients with stroke within 4.5 hours of stroke onset and recent studies suggest a longer time window for those with specific imaging findings. Patients participating in prior trials of IVT or EVT (which included IVT in eligible patients) were selected based on time from onset and imaging criteria with significant treatment effects and in some trials, dramatic increases in favorable outcomes. However, patients that did not meet inclusion criteria for the trials might have also benefited from EVT with a lesser but still significant effect. At the STAIR (Stroke Industry Academic Industry Roundtable) XI meeting, a workshop addressed the issue of establishing the outer limits of benefit from reperfusion therapy with the hope of expanding treatment to as many patients with stroke as possible. The participants included representatives from academia, industry, and government. The discussion focused on both EVT and IVT reperfusion and addressed 3 major topics: (1) what are the current limits for reperfusion therapy and how are these limits determined. (2) What is the minimum clinically important difference (MCID) that defines the limit, and (3) what methodologies are optimal for measuring the limits. Understanding that reperfusion and recanalization are not identical, for the purposes of this discussion the term reperfusion will be used acknowledging that in many cases there is considerable overlap between the 2 terms (Table 1).

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Table 1. Considerations in Treatment Limitations

Determinants of current limits	Defining limits	Measuring limits
Published data	Minimal clinical determinants	Conventional clinical trials
Societal guidelines	Goals of treatment	Platform trial design
FDA approval	Balancing risks vs benefit	Registry data
	Social values	Role of industry
	Resource allocation	Role of payers

FDA indicates Food and Drug Administration.

WHAT ARE THE CURRENT LIMITS FOR REPERFUSION THERAPY?

To explore the boundaries of benefit for reperfusion therapies, it is necessary to define the current limits based on evidence and practice (Table 1). Local standards are mostly determined by consensus guidelines published by professional societies and approved indications for drugs and devices regulated by the Food and Drug Administration (FDA). The American Heart Association 2019 updated guidelines recommend administration of IV alteplase for selected patients within 4.5 hours of stroke onset and suggest it may be beneficial in patients awakening with stroke symptoms or with unclear time of onset beyond 4.5 hours if diffusion magnetic resonance imaging demonstrates an abnormality smaller than 1/3 of the middle cerebral artery territory without fluid-attenuated inversion recovery signal change.[1] These guidelines recommend mechanical thrombectomy for stroke due to occlusion of the internal carotid artery or M1 segment of the middle cerebral artery within 6 hours of onset. Thrombectomy was also recommended for patients with stroke due to large vessel occlusion 6 to 16 hours from onset meeting eligibility criteria for the DAWN (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) studies and judged eligible based on DAWN criteria between 16-24 hours.[1] The European Stroke Organization consensus statement from the ESO-Karolinska Stroke Update in 2018 specifies IVT may be considered for patients with stroke of unknown time of onset or between 4.5 and 9 hours with penumbral mismatch identified by computed tomography or magnetic resonance imaging perfusion studies.[2] The recommendations are supported by high-quality randomized controlled trials as outlined in the guidelines. For both IVT and EVT the trials demonstrate a large treatment effect with number needed to treat of 10 to 19 for IVT[3,4] and 3 to 4 for EVT.[5–7] The highly significant benefit of reperfusion therapy applies to patients fitting the eligibility criteria for the trials. Although patients not meeting inclusion criteria for the trials might not benefit as much, even a lesser effect size could justify applying either IVT or EVT in additional populations. Current recommendations are based on factors, such as time from stroke onset, stroke severity, imaging characteristics, premorbid functional status, site of occlusion, and contraindications. Only 10% to 15% of patients with ischemic stroke receive IV alteplase,[8,9] and 3% undergo thrombectomy.[10] Expansion of indications for treatment to include a wider spectrum of patients with stroke would potentially improve outcomes from stroke and reduce disability for a disorder that is the leading cause of adult disability. Other aspects of reperfusion therapy, such as type of anesthesia, technical approach, device, or thrombolytic agent, also might warrant further exploration to expand the limits of current therapies. For areas of uncertainty, equipoise must be sufficient to justify enrollment of patients into randomized trials to provide high-quality data on which to base new treatment recommendations (Table 2).

Recommendations are as follows:

1. Existing guidelines recommend reperfusion therapies (IVT and EVT) in selected patients with acute stroke based on randomized controlled trials (RCT) demonstrating highly significant treatment effects. Subgroups of patients with acute stroke not included in the trials to date may benefit to a lesser but still clinically significant degree and should be explored with additional studies.

WHAT IS THE MCID TO DEFINE THE LIMITS?

The expansion of the limits of reperfusion therapy must consider the goals of treatment and the minimal effectiveness that balances risk and cost. Statistical significance based on *P* values is often tested in clinical trials to establish treatment effect; however, important differences between groups may be present but not reach statistical significance due to small sample sizes. When the number of participants is large, small clinically unimportant differences may reach statistical significance.

Table 2. Opportunities to Expand Current Limits

Areas of uncertainty	Opportunities
Type of window	Beyond 4.5 or 9 h for thrombolysis and beyond 24 h for thrombectomy
Baseline functional status	Baseline mRS of 3 and higher
Baseline clinical deficit	Baseline clinical deficit of NIHSS 5 or lower
Infarct burden	Baseline Alberta Stroke Program Early CT score of 5 or less or ischemic core >70 mL
Site of occlusion	Occlusions in the middle cerebral artery segment 2 or 3, anterior cerebral artery or posterior circulation

CT indicates computed tomography; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health.

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Another approach is to establish a minimally clinically important difference based upon the distribution of outcomes and compare with a reference baseline or consensus of a panel of experts.[11] MCID may contribute to calculation of power and sample size when designing trials. Lin and Saver[12] recently used the latter methodology to estimate an MCID for reperfusion by mechanical thrombectomy devices for acute ischemic stroke. A difference between devices of 3.1% to 5% for thrombolysis in cerebral infarction 2b/3 reperfusion within 3 passes was considered a minimal threshold. A similar approach might be appropriate for establishing the MCID for defining the limits of reperfusion therapy for acute stroke. The consideration should be the minimally important difference in outcomes between treatment and control groups. Studies have found that for a simply delivered treatment, the MCID for functional independence (modified Rankin Scale score of 0–2) at 3 months post-stroke is as low as 1.1% to 1.5%.[13,14] However, for a labor and capital intensive intervention like EVT, the MCID for functional outcome might be higher. The randomized trials of IVT and EVT to date demonstrate large treatment effects well above what many would consider a minimal acceptable benefit. Both IVT and EVT increase the risk of intracerebral hemorrhage, a potentially devastating result often leading to clinical worsening. Angioedema is an occasional side effect of IVT and access site complications, dissection, or vessel perforation may occur with EVT. The possibility of adverse events with clinical consequences must be considered in determining MCID. In addition, there are significant costs to the health care system in establishing capabilities for reperfusion therapies and dealing with any adverse events. In estimating an MCID, these issues should become part of the calculation with a larger MCID necessary for treatments with greater risk and health care costs.

Several factors should be considered in determining MCID. The value of specific outcomes may differ across populations, ethnic groups, and geographic areas. The utility weighted modified Rankin Scale is an example of an outcome measure that adjusts for community assessment of outcomes but may not be consistent in all settings.[15,16] The opinions of patients and families regarding stroke outcomes are additional elements that clinicians should consider. Quality of life data are another method of incorporating societal norms into outcomes and could contribute to determination of MCID. Cultural values also vary across populations. For example, in some cultures, modified Rankin Scale 4 or 5 might be considered acceptable, whereas others believe that is an unacceptable outcome. In addition, up to 50% of adults view the prospect of a severe disabling stroke as "worse than death" which may motivate opting for acute treatments with low chance of success despite high risk of death.[17] These cultural standards must also be assessed in the context of societal burden and cost-effectiveness.

The possibility of harm is an important aspect of probing the limits of reperfusion therapy. A greater probability of harm should raise the threshold for determining a clinically important treatment benefit. Both the number needed to treat and number needed to harm should be part of the formula, and some outcome measures incorporate both benefit and harm. Higher number needed to treat is more acceptable for treatments with low number needed to harm. The treatment effect must be sufficient to convince society that it should be applied on a population scale. Weighing the risks and benefits for individual patients depending on age, comorbid conditions or other factors requires an understanding and acceptance of the importance of treatment effects.

Whether cost should be included in determining treatment limits is less clear. From a societal and health care policy perspective, overall cost and cost per beneficial outcome are important factors. However, if the issue is whether treatment benefits patients and improves outcomes, cost might be factored in separately. The opinion of experts asked to reach a consensus on MCID likely consciously or subconsciously reflect harm and cost, but other methods for determining MCID do not. A critical consideration must be the acceptance of the determined MCID by the medical and nonmedical community including government agencies and payers. The treatment effect must be sufficient to convince society that it should be applied on a population scale. There are many established measures of cost-effectiveness and treatments that do not reach a threshold for cost-effectiveness should not be supported. Weighing the risks and benefits for individual patients depending on age, comorbid conditions or other factors requires an understanding and acceptance of the importance of treatment effects.

The MCID concerns for industry differ in some ways from the academic community. An MCID sufficient for the medical and patient community to consider a treatment beneficial may not be sufficient to achieve FDA approval for drugs or devices. Historically a 10% difference between groups or devices has been a good rule of thumb justifying decisions regarding substantial business investments. Recently proposed ongoing EVT and IVT trials use a lower MCID of 5%. Although not necessarily relevant to the biological limits of treatment, industry views must be considered in translating trial findings into practice.

Recommendations are as follows:

1. MCID is an important consideration in determining the limits of reperfusion therapies.
2. In addition to expert opinion, societal factors, patient and family opinions, and quality of life assessments should be factored into outcome measures and the determination of MCID and may vary across populations.
3. Acceptance in the medical community and FDA approval may require different thresholds of

significance and MCID. Trials exploring the limits of reperfusion therapies should consider both of these goals in designing protocols and choosing outcome measures.

WHAT METHODOLOGIES ARE OPTIMAL FOR MEASURING THE LIMITS?

Results from RCTs remain the highest level of evidence and previous results have demonstrated the benefit of both IVT and EVT in acute ischemic stroke. The pooled analysis of IVT and EVT studies establishes the current indications based on the characteristics of patients included in the trials. IVT improves outcomes for selected patients up to 4.5 hours from stroke onset with computed tomography imaging and up to 9 hours with favorable magnetic resonance imaging or perfusion imaging parameters. EVT trials show improved outcomes in selected patients up to 24 hours from onset. These completed studies include only patients with specific core size, computed tomography or perfusion findings, site of occlusion, collateral adequacy, baseline disability, age, or comorbidities. Exploring patients excluded from these trials with individual RCTs for each category would require an enormous effort. A platform trial has been proposed to probe all eligibility limits of EVT through a common mechanism maximizing the utility of each patients' data and minimizing cost and organizational effort. The platform design has worked well in other areas, such as cancer, glioblastoma, and Alzheimer disease.[18] Whether sufficient qualified sites are available to recruit adequate patients for EVT trials is unclear. Given the likelihood of smaller treatment effects, large patient numbers will be needed. Including smaller centers with fewer patients and less resources as well as international sites in the platform design is challenging. International barriers include transfer of data, privacy laws, and regulatory differences. A possible solution is to partner with other international networks using the same study design sharing common data elements and potentially a single data repository. If successful, the platform concept might be extended to IVT. The same efficiencies of patient data and organization would apply to IVT. Until these research tools mature, other sources of data on patients not represented in RCTs include registries and large pragmatic trials.

A registry component is integrated into the platform proposal for EVT evaluation providing a means of exploring outcomes in subgroups of EVT patients treated outside of guidelines and including results of best medical therapy without EVT. These data would allow generation of hypotheses for extending the limits of therapy and increase the likelihood of demonstrating benefit. If the comparator for EVT or IVT is optimal medical management, the elements of such management should be documented in the registry entries. Adequate oversight and quality control are crucial to the validity of such a database. Centralized review of imaging and adjudication of end points while challenging, would further enhance the value of a registry component.

Pragmatic therapeutic trials have contributed to knowledge in other fields.[19] There are clear drawbacks to such trials, but the large number of patients and minimal exclusions reduce bias and improve generalizability outside of specialized centers that are typically included in RCTs. Given the widespread acceptance of reperfusion therapies, this approach should be viable and potentially informative. An aspirational goal would be to generate algorithms that predict an individual's probability of experiencing various functional outcomes by incorporating multiple patient, stroke, and treatment associated factors. Both registries and large pragmatic trials could contribute to databases amenable to analytics using artificial intelligence and machine learning sufficient to accomplish this goal.

Partnering with industry to explore the limits of reperfusion therapies and potential innovations has tangible advantages. Industry experience with and funding for navigating FDA approval pathways is invaluable for bringing new drugs and devices to market. Although there are considerable barriers to such collaboration including data sharing, conflicting goals, and speed of completion, under the right circumstances, both parties should benefit from such collaboration. International industry entities introduce additional complications such as regulatory oversight and country-specific regulations. The stroke community should continue to explore ways to bring all academic and industry partners to work together toward common goals.

Recommendations are as follows:

1. Innovative methodologies such as platform trials to explore the limits of reperfusion therapies are encouraged to increase efficiency and make best use of individual patient outcomes.
2. Registry data should supplement RCTs to generate additional hypotheses and extend limits but must apply standardized protocols and include adequate quality controls.
3. Large pragmatic trials have a role in addressing generalizability and expected results in routine practice.
4. Large databases incorporating results of registries and pragmatic trials should be explored to create algorithms to predict outcomes.
5. Industry/academic partnerships are critical to bringing new approaches and indications to fruition through the FDA approval process.

CONCLUSIONS

The current limits of IVT and EVT are based on multiple RCTs and defined by consensus guidelines published by major US and international societies. It is likely that many patients outside the existing guidelines benefit from reperfusion therapy but possibly with less robust treatment effect. Exploring the outer limits of reperfusion therapy should consider cultural, regional, and patient-specific norms. Cost is an important consideration that ultimately must be factored into treatment selection but differs from biological efficacy. Beyond statistical significance, the MCID should drive exploration of reperfusion benefit. A platform design for evaluation of multiple aspects of EVT has been proposed and offers advantages in maximizing the value of each entered patient and increasing efficiencies. In addition to RCTs, registries and pragmatic designs hold the prospect of contributing valuable data supporting and supplementing results of RCTs. Industry partners should be incorporated into the process of expanding indications for reperfusion therapies to facilitate translation of results into clinical practice.

ARTICLE INFORMATION

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Disclosures

Dr Wechsler is a Consultant at Silk Road Medical. Dr Jovin is an advisor/investor for Anaconda, Route92, VizAi, FreeOx, Blockade Medical, and Methinks. He received personal fees in his role on the Data Safety Monitoring Board and steering committee from Cerenovus and on the screening committee for Contego Medical. He received stock as advisory board member for Corindus. He received grant support for Medtronic and from Stryker Neurovascular in his capacity as Principal Investigator for the DAWN (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and AURORA (Analysis of Pooled Data From Randomized Studies of Thrombectomy More Than 6 Hours After Last Known Well). The other author reports no conflicts.

APPENDIX

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