

Practicing Evidence-Based Stroke Medicine

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The practice of evidence-based medicine depends on several steps: a basic science derived understanding of disease pathophysiology, epidemiological research, and the results of well-conducted and appropriately analyzed randomized clinical trials (RCTs). The approval of new therapies by regulatory agencies is also based largely on RCT determination of the safety and therapeutic efficacy of drugs and devices. Once a new therapy is approved for use in clinical practice, clinicians typically begin to use it in a manner which mirrors the clinical trial design, for example, in the population for who risk and benefit have been established. It must be acknowledged that in the United States and in other countries, clinicians have leeway in their therapeutic decision making and it is not uncommon for therapies to be used for situations not tested in the RCTs that led to approval, the so-called off-label use. The off-label use of stroke-related therapies is relatively common, and we will consider the appropriateness of doing this in 3 common clinical scenarios.

Performing Thrombectomy

The relatively recent demonstration of the efficacy of thrombectomy within 6 hours of stroke onset in 6 well-conducted RCTs provides convincing evidence that this treatment is highly effective in improving functional outcome.^{1,2} These RCTs carefully selected patients with small-to-moderate ischemic cores, primarily by assessing the pretreatment Alberta Stroke Program Early CT Score (ASPECTS) on a noncontrast head CT, but computerized tomography perfusion (CTP) and diffusion-weighted magnetic resonance imaging were also acquired in some patients. In these trials, the median baseline ASPECTS score was 9, indicating a very small ischemic core and in 3 of the trials a baseline score of ≤ 5 was an exclusion. Even in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), a trial which did not specify an ASPECTS exclusion criterion, the median baseline score was 9. A minority of patients in the trials had scores of 6 to 7, and very few had scores of ≤ 5 . The inclusion of patients with a proximal vessel occlusion proven by computerized tomographic angiography or magnetic resonance angiography and small/moderate ischemic core ensured that a large region of

at risk ischemic tissue, the ischemic penumbra, was present before thrombectomy. This factor along with the very high rate of vessel recanalization achieved and rapidity of vessel opening led to the dramatic therapeutic success.³ The US Food and Drug Administration approval of the Solitaire device mentions that it should be used in ischemic patients with a smaller infarct core. In clinical practice, a wide range of strategies is being used to identify patients for thrombectomy within 6 hours of stroke onset. In some centers, after demonstration of a proximal vessel occlusion and a computerized tomography (CT) with no evidence of hemorrhage, almost all patients undergo thrombectomy with no attempt to identify the extent of the ischemic core by ASPECTS, CTP, or diffusion-weighted magnetic resonance imaging. Patients with a very large hypodense region qualitatively identified are presumably excluded. Proponents of this strategy would argue that thrombectomy is highly effective as we do not yet know how large an ischemic core at baseline identifies patients who will no longer respond to thrombectomy. In other centers, the ASPECTS score is used to identify thrombectomy candidates. Unfortunately, the ASPECTS score has low interobserver reliability, and conspicuity on head CT scanning is related to the amount of radiation used to acquire the scan.^{4,5} Most centers use a reduced dose of radiation to acquire their head CT scans so the literature supporting the use of ASPECTS may not reflect routine practice. An argument for using CT ASPECTS would be that even if the score is off by 1 to 2 points most treated patients would still be in the ≥ 6 range as in the RCTs. Some centers use CTP to either qualitatively or quantitatively identify the ischemic core. Using CTP is probably more precise than CT ASPECTS, but ischemic core identification is dependent on the parameter used to identify it and the threshold that is considered to represent the ischemic core. In the past, cerebral blood volume maps were widely used to identify the ischemic core, but these are notoriously inaccurate.⁶ Currently, cerebral blood flow (CBF) or mean transit maps are widely used to identify the ischemic core, and many studies support a threshold of CBF $< 30\%$ of the contralateral hemisphere as a reasonable threshold for estimating the extent of the ischemic core.⁷

This approach was used in the recently reported diffusion-weighted magnetic resonance imaging and CTP Assessment in the DAWN trial (Triage of Wake-up and Late Presenting Strokes Undergoing Neurointervention) that demonstrated the remarkable therapeutic efficacy of thrombectomy with the Trevo device in the 6- to 24-hour time window in stroke patients with ischemic cores of < 20 or 30 mL (depending on their age) with an National Institutes of Health Stroke Scale score between 10 and 20 and an ischemic core of ≤ 50 mL with an National Institutes of Health Stroke Scale score > 20 .⁸ The regulatory approval of the Trevo device for 6- to 24-hour patients will likely include a requirement for ischemic core

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volume measurement. For thrombectomy candidates in the <6-hour time window, we do not know the extent of CBF-derived ischemic core volume on CTP that is no longer responsive to therapy. Clinicians should at least attempt to identify the extent of the ischemic core before thrombectomy. If the ASPECTS score is used and centers are confident in their ability to derive the score accurately, patients with a score of ≤ 5 should not be treated. If CTP is used, then CBF maps using the threshold of ischemic tissue with a CBF of $\leq 30\%$ should be used to identify the volume of ischemic tissue. Some centers may wish to exclude patients with a large ischemic core volume, perhaps >70 or even 100 mL. Other centers may treat patients irrespective of the CTP-derived core volume. We encourage centers to maintain an outcome registry that relates the pretreatment imaging and clinical characteristics to 90-day modified Rankin Scores so that data can be pooled for analysis and the volume of ischemic core not amenable to thrombectomy identified. For patients beyond 6 hours, the inclusion criteria used in the DAWN trial should be adhered to in most cases or it is likely that clinical practice outcomes will not recapitulate the trial results. For both early and late thrombectomy patients, the rapidity of the procedure and extent of vessel opening should be maximized because time is brain.

Combination Antithrombotic Therapy

A second area of concern on the practice of evidence-based stroke medicine is antithrombotic therapy. For secondary stroke prevention in patients with noncardioembolic ischemic stroke, 3 antiplatelet drugs, aspirin, clopidogrel, and aspirin plus dipyridamole, are approved in the United States for secondary stroke prevention.⁹ The use of combining aspirin and clopidogrel for enhancing secondary stroke prevention was tested in several RCTs with long-term follow-up, and any benefits on prevention of ischemic events were negated by major bleeding side effects. The SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) did demonstrate that the combination of aspirin plus clopidogrel significantly reduced the 90-day rate of ischemic outcome events in patients with symptomatic high-grade intracranial stenosis and the CHANCE (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) also demonstrated a reduction of 90-day ischemic events with this combination compared with aspirin alone in a more general Chinese mild stroke and transient ischemic attack population.^{10,11} In both trials, bleeding risk with combination therapy used for 90 days was reasonable. Therefore, the only RCT data currently available to support using the combination of aspirin and clopidogrel for ischemic stroke prevention are 90-day use, and it is currently unclear that this combination is efficacious in a non-Chinese patient without high-grade intracranial stenosis or beyond the 90-day time period. The ongoing POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial) will provide evidence concerning the 90-day efficacy and safety of the clopidogrel/aspirin combination in patients with a broader range of ethnic and racial backgrounds. Despite the lack of evidence, it is not uncommon for clinicians to use this combination in ischemic stroke or transient

ischemic attack patients who have their event on aspirin or clopidogrel alone and then continue treatment indefinitely. Similarly, in patients with atrial fibrillation who have a stroke or transient ischemic attack while taking warfarin or one of the newer anticoagulants, some clinicians add an antiplatelet drug to the anticoagulant after the event. There is no evidence that this combination reduces the risk of subsequent ischemic events and clear evidence that the major bleeding risk is significantly increased.⁹ Both of these therapeutic practices should be avoided unless future RCT results demonstrate efficacy and safety.

Use of Statins After Ischemic Stroke

A third area of concern is the broad use of statins after ischemic stroke in patients who were not studied in RCTs and in whom statins are not recommended in practice guidelines. The primary RCT providing evidence about statin therapy reducing the risk for recurrent events was SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels).¹² In this study, atorvastatin significantly reduced the risk for recurrent stroke in patients with large artery and lacunar stroke, but patients with cardioembolic stroke were excluded. The most recent American Heart Association secondary stroke prevention guidelines recommend high-dose statin therapy in patients with atherothrombotic stroke, but no recommendation is correctly made for cardioembolic stroke unless they have another indication for statin therapy such as coronary artery disease, an unfavorable lipid profile or a cardiovascular risk stratification score suggesting a substantial risk for cardiovascular events.⁹ Despite the RCT results and American Heart Association guideline recommendation, high-dose statins are routinely prescribed in cardioembolic stroke patients who have no other indication for them. A recent observational study from a large database evaluated the risk of recurrent stroke in patients with or without atrial fibrillation who took statins after their stroke.¹³ The risk of recurrent stroke was strongly related to adherence with the statin prescription and adherence in both groups, suggesting that statins may reduce recurrent stroke risk in stroke related to atrial fibrillation. Though intriguing, this study is not definitive, and the results may have been affected by bias and confounding. An RCT will be needed to provide evidence that statins reduce recurrent stroke risk in atrial fibrillation-related stroke.

The stroke field has seen an increasing number of positive RCTs that have led to remarkable, proven treatment advances for prevention and acute treatment. Clinicians need to carefully read the results of these RCTs and be aware how they were incorporated into the regulatory approval of these therapies. They can then decide how to use them in their clinical practices. In most situations to truly practice evidence-based medicine, clinicians should try to replicate how the therapies were evaluated in the RCTs and practice accordingly. Of course, clinical judgment allows for exceptions based on individual circumstances of the patient. This is the art of medicine. At *Stroke*, we will continue to provide our readers with expert evaluations of important RCTs that appear in other journals, so that clinicians can have help in how they interpret trial results and in their consideration as to how to use the results in daily practice.

Disclosures

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