Optimizing Systems of Care for Endovascular Thrombectomy in Ischemic Stroke
Drip and Ship Versus Mothership

In this issue of Circulation, Smith and colleagues report the impressive uptake in endovascular thrombectomy for ischemic stroke in the United States since the publication of positive randomized trials in 2015. However, there is substantial capacity to further increase the proportion of patients treated. This relates mainly to the structure of the healthcare system that has contributed to variable uptake of endovascular therapy globally, even within developed countries. Smith et al found an almost 2-fold variation in rates of endovascular thrombectomy between states in the United States. The crucial impact of systems of care is also highlighted by Froehler and colleagues, who present data from the STRATIS registry (Systematic Evaluation of Patients Treated With Stroke Devices for Acute Ischemic Stroke) demonstrating substantially worse outcomes in patients requiring interhospital transfer to access endovascular thrombectomy, directly linked to delayed time to revascularization.

The proportion of patients with ischemic stroke eligible for endovascular thrombectomy is currently unknown, and clinicians' perceptions of eligibility continue to evolve with new evidence and greater familiarity. The HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) individual patient data meta-analysis demonstrated benefit across a broad range of clinical and imaging subgroups that extend well beyond the current American Heart Association/American Stroke Association Class 1 recommendation. Large vessel occlusion (LVO) status is not recorded in the Get With The Guidelines database, so Smith and colleagues used a construct of "potentially eligible" patients, defined as arrival <4.5 hours after last known well time and National Institutes of Health Stroke Scale score ≥6. With this definition, only 27% of potentially eligible patients at endovascular-capable hospitals received thrombectomy. Obviously, this is an overestimate of the proportion of patients with LVO within 4.5 hours (National Institutes of Health Stroke Scale score ≥6 has ≈90% sensitivity but only ≈35% positive predictive value for LVO). Additional patients would be deemed unsuitable because of poor premorbid function.

This potentially eligible proportion was also based on a conservative 4.5-hour time window for treatment. There was evidence of benefit out to 7.3 hours in HERMES data, and substantial expansion of that time window is expected on the basis of the eagerly awaited DAWN trial (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; clinicaltrials.gov NCT02586415). These trials, stopped early because of efficacy, successfully used imaging selection to identify patients who benefit from reperfusion up to 24 hours.

One population-based estimate of the proportion eligible for endovascular thrombectomy, before the extended window trials, suggested that 13% of all ischemic strokes (22 ischemic strokes per 100,000 person-years) would have LVO, present to hospital within 5 hours (to allow treatment within 6 hours), and have...
acceptable premorbid function (modified Rankin Scale score, 0–3) and no large established infarct.\textsuperscript{6} Even without time window expansion, this proportion is twice that currently treated in endovascular-capable centers in the United States (7.5%) and \texttimes{}4 times the proportion treated when all hospitals in the Get With The Guidelines database were considered (3.3%). The true proportion of patients currently treated is likely to be lower still in hospitals not participating in the registry.

The key findings from the STRATIS registry were that patients who required interhospital transfer for thrombectomy achieved reperfusion a median 109 minutes later than direct presenters and had an \texttimes{}8 lower absolute probability of independent outcome. These data are consistent with results from the HERMES meta-analysis, in which onset to reperfusion time was 2 hours longer in patients requiring interhospital transfer\textsuperscript{7} and real-world data from Melbourne, Australia, which also showed a 2-hour delay related to interhospital transfers.\textsuperscript{9} No data were available in STRATIS on the proportion of patients referred for treatment by nonendovascular hospitals compared with endovascular-capable hospitals. However, the Get With The Guidelines data suggest that there is substantial attrition in the proportion of potentially eligible patients actually treated among those who do not present directly to an endovascular-capable center. The combined effect of fewer patients receiving treatment and worse outcomes in those who are treated is that the true outcomes for patients with LVO presenting to nonendovascular capable hospitals are likely to be substantially worse than indicated by STRATIS.

These data demand a substantial change in the way we manage stroke. There may be lessons from the transition to endovascular procedures in cardiology in previous decades. However, the incidence of ST-segment-elevation myocardial infarction\textsuperscript{10} is \texttimes{}3 times that of LVO ischemic stroke. Percutaneous coronary intervention generally also has fewer technical challenges in vascular access and potential complications. It is therefore unlikely that uncontrolled proliferation of endovascular-capable centers is the best option for service delivery. Procedural volume and patient outcomes are clearly related,\textsuperscript{11} which favors a concentration of expertise at centers that are deliberately located to provide optimal geographic coverage. This central control of health system delivery is uncommon, particularly in the United States, but has been achieved for trauma, which may act as a useful precedent when lobbying for change.

There is much room for improvement in optimizing hub-and-spoke transfer networks through formalized protocols for eligibility, referral, and transfer and a reduction in “door-in-door-out time.”\textsuperscript{9} These approaches may minimize the referral attrition seen in Get With The Guidelines and the major delays leading to worse outcomes seen in transferred patients in STRATIS. Efficient use of brain imaging is one of the key elements in streamlined hub-and-spoke workflow. The positive endovascular trials all used computed tomography (CT) angiography (CTA) as an inclusion criterion. However, the current approach in many systems involves only noncontrast CT at the primary stroke center and transfer of patients with severe syndromes and hyperdense arteries. Definitive imaging then occurs on arrival at the endovascular-capable center, and if the neurointerventional team is activated only at that point, this introduces major delays in achieving reperfusion. It also leads to many futile transfers and, if activation does occur before imaging, unnecessary activations of the neurointerventional team. A more efficient approach is to immediately follow noncontrast CT with CTA of the arch to cerebral vertex at the initial hospital. Universal CT/CTA also identifies patients with LVO despite milder clinical symptoms who are at risk of subsequent clinical deterioration if untreated.\textsuperscript{12} Other benefits of routine CTA include making a positive diagnosis of stroke and identifying stroke mechanism. CTA is well within the hardware capability of contemporary CT scanners, and staff require minimal training. However, extra imaging at the initial hospital must not create undue delay, and the images must be immediately available for electronic review by the receiving stroke and neurointervention teams.

The additional of CT perfusion has diagnostic benefits,\textsuperscript{13} provides additional confidence in telemedicine scenarios, and, on the basis of DAWN and DEFUSE 3, will be particularly critical for patients requiring long transfers that may put them outside 6 hours by the time of treatment. Definitive imaging at the initial hospital allows appropriate activation of the neurointervention team and reduces door-to-puncture time on arrival. In many cases, the patient can proceed directly to angiography without further cross-sectional imaging, unless there has been major clinical deterioration or an unexpectedly long transfer time.

Although optimizing the existing hub-and-spoke networks is the simplest solution, the ideal approach to the system of care would involve recognition of LVO patients in the field and direct transport to an endovascular-capable center. Definitive LVO diagnosis before hospital arrival is enabled by CT-equipped mobile stroke units. These are increasing in number but are unlikely to form a widespread solution in the near future. There has been a proliferation of clinical triage scales that aim to allow bypass of patients with suspected LVO to an endovascular center. Although fairly sensitive to the diagnosis of LVO, the main challenge has been specificity, leading to the concern that patients who require only intravenous thrombolysis may receive delayed treatment as a result of bypassing their nearest hospital. The RACECAT randomized trial (Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion; NCT02795962) is testing one of these clinical triage scales across the region of Catalonia in Spain. Some patients may be bypassed from regions with a 2-hour travel time to the nearest endo-
vascular center, and the results are keenly awaited. However, the American Heart Association/American Stroke Association Mission: Lifeline program has already recommended that patients with severe stroke within 6 hours of stroke onset should be bypassed to an endovascular-capable hospital if this will incur no more than 15 minutes of additional travel time and not cause them to miss the thrombolysis treatment window.

It is reassuring that the hypothetical modeling from STRATIS indicates that the minimal thrombolysis delay with bypass to an endovascular center was greatly outweighed by faster times to revascularization. Furthermore, the added value of thrombolysis in patients who can be rapidly reperfused by endovascular thrombectomy is uncertain and being examined in clinical trials.

Endovascular thrombectomy for ischemic stroke is an immensely powerful treatment to reduce disability for patients with the most severe strokes. The indications are continuing to expand, but it is already clear that a large group of potentially eligible patients are not accessing optimal treatment. Furthermore, system-related delays are compromising outcomes for those patients who do access endovascular thrombectomy. A system-wide, centralized effort will be required to optimally distribute resources, and stroke physicians will need to engage in the political process required to achieve reengineering of the care delivery system.15

DISCLOSURES
None.

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FOOTNOTES

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REFERENCES


