# Editorial

# Variance of Imaging Protocols for Patients With Suspected Acute Ischemic Stroke Because of Large-Vessel Occlusion

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The benefits of thrombectomy in patients with stroke with a proximal large-vessel occlusion (LVO) who had initiation of the procedure within 12 hours of stroke onset (most of the patients included within 6 hours) were clearly established by 6 randomized clinical trials published several years ago.[1–6] The beneficial effects of thrombectomy with LVO were extended to ≤24 hours in carefully selected patients in the more recently published DAWN (diffusion-weighted imaging or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Stroke Undergoing Thrombectomy With Trevo) and DEFUSE-3 trials (The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke).[7,8] In all of the trials, a head computed tomography (CT) or magnetic resonance imaging was performed to exclude an intracerebral hemorrhage and to estimate the extent of the ischemic core with an Alberta Stroke Program early CT score (ASPECTS). In 4 of 6 of the earlier time window randomized clinical trials, an ASPECTS score <6 or 7 was an exclusion criterion in 3 trials, and the median ASPECTS score was 9 in 3 trials where it was reported and 7 and 8 in another trial. In the EXTEND IA trial (Extending the Time for Thrombolysis in Emergency Neurological Deficits With Intra-Arterial Therapy), CT perfusion (CTP) was to identify the ischemic core and penumbra and only included patients with an ischemic core of <70 mL.[2] The SWIFT PRIME trial (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment) initially required penumbral imaging be acquired to determine ischemic core and penumbral volumes but amended enrollment criteria to allow enrollment of patients without it.[4] Eighty-one percent of the enrolled patients had penumbral imaging, and 84% of those patients had a target mismatch profile. All of the trials used either CT or MR angiography to identify LVO in the distal internal carotid artery or proximal portion of the middle cerebral artery. In the 2 late window trials, CTP or diffusion/perfusion magnetic resonance imaging was used to include/exclude patients, and the trials only included patients with a small-to-moderate ischemic core. The median value was 9.4/10.1 mL in DEFUSE-3 and 7.6/8.9 mL (thrombectomy/control) in DAWN.[7,8] The risk of symptomatic intracranial hemorrhage was acceptably low and ranged from an absolute value of 3% less to 3% more with thrombectomy in the earlier window trials. In the 2 later window trials, an absolute 3% increase in symptomatic intracranial hemorrhage was seen and an almost doubling of the risk was observed, 3% versus 6% in DAWN and 4% versus 7% in DEFUSE-3.

Both the early and late time window thrombectomy trials were either designed or performed in a manner to maximize the chances of demonstrating successful treatment effects with thrombectomy. The trials either required a small/moderate ischemic core as identified by the ASPECTS score or by CTP and diffusion-weighted imaging or actually enrolled such patients. In the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands), the median baseline ASPECTS score was 9, despite not specifying the exclusion of patients with low ASPECTS scores.[1] In the THRACE trial (Thrombectomie des Arteres Cerebrales) most patients (74%) were evaluated by magnetic resonance imaging at baseline and the remainder by CTP. All patients received intravenous tPA (tissue-type plasminogen activator). Inclusion was not based on baseline lesion size on either modality, and the trial included 14% of patients with a baseline ASPECTS score of 0 to 4 and 13% of patients with a diffusion-weighted imaging lesion volume >70 mL.[6] Interpreting the benefits of thrombectomy in the THRACE trial is problematic because 59 of 204 (28%) who initially received tPA did not have the thrombectomy performed, predominantly because of clinical improvement, 35 patients, or complete recanalization, 18 patients. Benefit should not be attributed to thrombectomy in these patients who either improved clinically and did not need it or recanalized and likely had a good outcome, despite intention to treat. Therefore, determining whether thrombectomy is beneficial in patients with larger ischemic cores in THRACE is uncertain.

What are the conclusions one can draw based on all the recent data?

1. The natural history of disease for patients with acute ischemic stroke because of LVO is dismal.
2. Thrombectomy is a robust and highly efficacious treatment (number needed to treat of 2.6 for improving the modified Rankin scale score by 1 point at 90 days. This level of number needed to treat falls in the category of antibiotics and antiepileptic drugs).
3. The complication rate of thrombectomy is low. The presence or absence of intravenous tPA use does not significantly affect the complication rate.
4. Time is brain. Not only does time from onset matter, workflow within the hospital is also important, and all efforts should be made to make the performance of thrombectomy as efficient as possible.[9]



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**(*Stroke*. 2018;49:00-00.**
**DOI: 10.1161/STROKEAHA.118.022191.)**



***Stroke* is available at http://stroke.ahajournals.org**
**DOI: 10.1161/STROKEAHA.118.022191**

**Table 1. Nineteen Expert Responses to Case Scenarios A and B**

| Scenario | Directly to Angiography | Directly to Angiography if ASPECTS >5 | CT/CTA/mCTA if Worse | CT/CTA/mCTA/CTP | MRI |
|---|---|---|---|---|---|
| A* | 7 | 2 | 6 | 3 | 1 |
| B† | 5 | 1 | 1 | 8 | 2 |

For scenario B, there are only 17 responses because 2 participants do not receive patients with long transfer times. ASPECTS indicates Alberta Stroke Program early CT score; CT, computed tomography; CTA, computed tomographic angiogram; CTP, computed tomographic perfusion; mCTA, multiphase computed tomographic angiogram; MRI, magnetic resonance imaging; and NIHSS, National Institutes of Health Stroke Scale.

*A patient with a high NIHSS score documented 2 h from stroke onset at an outside hospital is being transferred to you and the transfer will take 30 min. The patient had an unremarkable head CT and a CTA that you reviewed remotely, and it demonstrates an M1 occlusion.

†A patient with a high NIHSS score documented 2 h from stroke onset at an outside hospital is being transferred to you and the transfer will take 2 h. The patient had an unremarkable head CT and a CTA that you reviewed remotely, and it demonstrates an M1 occlusion.

5. The quality of reperfusion matters. Traditionally, modified Thrombolysis in Cerebral Infarction 2b/3 has been taken as good reperfusion. There is a move toward using Thrombolysis in Cerebral Infarction 2c/3 as good reperfusion. Better reperfusion correlates with better outcome.[10]
6. Patients should not be excluded from being offered thrombectomy based on any of these taken in isolation: age, sex, time from onset, site of occlusion (internal carotid artery or M1), size of core on CTP, and moderate-to-good ASPECTS (data from HERMES collaboration suggest benefit of treatment even in patients with large core on CTP or low ASPECTS) in the earlier time window.[11–13] Although it must be acknowledged that currently there is uncertainty about the treatment benefits of thrombectomy in patients with low ASPECTS scores or large ischemic cores on CTP or diffusion magnetic resonance imaging. Randomized clinical trials specifically designed to address the limits where thrombectomy is no longer beneficial are needed. For the late time window, there are 2 recent trials demonstrating the benefit of thrombectomy over standard medical care in carefully selected patients. It is important to note that these trials did not test patient selection based on criteria A versus criteria B (eg, selection of patients based on ASPECTS and collaterals versus selection of patients based on predefined CTP criteria).

In addition, it is reasonable to assume that most thrombectomy centers will push for increased speed of procedure performance and more efficient organization, it is likely that workflow within hospitals will continue to improve. Similarly, with better training, technique, and technology, the extent of reperfusion will also improve compared with the trial data. These enhancements should translate into better clinical outcomes and more lenient patient inclusion criteria in the future. Thus, in patients with suspected LVO, imaging should be performed with the highest possible efficiency to allow for expedient decision-making. The aims of imaging should be (1) to exclude hemorrhage, (2) to confirm LVO, and (3) to show imaging features, such as a low ASPECTS score or large ischemic core volume that in some patients may preclude a reasonable outcome even if the vessel could be quickly opened and substantial reperfusion established. This third criteria should be put in perspective of other clinical information, such as patient's age, premorbid status, etc, which have been shown to affect functional outcome.[12,13]

The wide range of baseline imaging studies performed in the early time window thrombectomy trials has led to discrepant approaches to the baseline imaging evaluation of patients with stroke who are being considered for this treatment. This is exemplified by presentations at recent stroke conferences, such as the recent International Stroke Conference in Los Angeles and by discussions with vascular neurology and neurointerventional colleagues. To determine how leaders in the stroke field are currently imaging patients with stroke who are potential thrombectomy candidates who either present to their home institution or who are transferred there, we surveyed 2 senior authors from the 6 early window thrombectomy trials, as well as DAWN and DEFUSE-3. We also surveyed 2 senior authors from the THERAPY trial (The Randomized Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke) and endovascular therapy for acute ischemic stroke: PISTE randomized controlled trial (The Pragmatic Ischemic Stroke Thrombectomy Evaluation).[14,15] Of the 20 authors contacted from the United States, Canada, and

**Table 2. Nineteen Expert Responses to Case Scenarios C, D, and E**

| Scenario | Directly to Angiography | CT/CTA/mCTA* | CT/CTA/mCTA/CTP | MRI/MRA (Includes DWI) |
|---|---|---|---|---|
| C† | 0 | 10 | 7 | 2 |
| D‡ | 0 | 2 | 13 | 4 |
| E§ | 0 | 2 | 13 | 4 |

CT indicates computed tomography; CTA, computed tomographic angiogram; CTP, computed tomographic perfusion; DWI, diffusion-weighted imaging; ED, emergency department; mCTA, multiphase computed tomographic angiogram; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; and NIHSS, National Institutes of Health Stroke Scale.

*Multiphase CT angiography.

†A patient presents to your hospital with a high NIHSS score 2 h after symptom onset.

‡A patient presents to your hospital with a high NIHSS score 8 h after symptom onset.

§A patient presents to your hospital with a high NIHSS score upon awakening and was last known to well 10 h before evaluation in the ED.

several European countries, 19 responded to the survey. The case scenarios provided to them are included in Tables 1 and 2 as are their responses on the type of imaging they would perform before proceeding to angiography. For patients presenting early after stroke onset, who are rapidly transferred to the thrombectomy center (scenario A), approximately half of the respondents would proceed directly to angiography, and some would repeat a CT/CT angiogram or multiphase CT angiogram, if the patient clinically worsened during transport. Only 4 of 19 would do advanced imaging before proceeding. For scenario B with early presentation after stroke onset, but a much longer transport time, only 6 of 17 would proceed to angiogram without additional imaging with most doing advanced imaging. For patients directly admitted to a thrombectomy capable hospital early after stroke onset (scenario C), who obviously had no imaging before presentation, the respondents were essentially equally divided between doing advanced imaging or just a head CT and CT angiogram/multiphase CT angiogram to determine whether patients were thrombectomy candidates. The respondents had a range of exclusion criteria for such an early time window patient with some excluding patients with an ASPECTS score <5 or 6 and others not having any ASPECTS exclusion criteria. One respondent excluded patients with a diffusion-weighted imaging lesion volume >100 mL. For patients presenting to a thrombectomy center 8 hours after stroke onset or with a wake-up stroke (scenarios D and E) only 2 of 19 respondents did not perform advanced imaging, and most of those who did would exclude patients with a large ischemic core using the criteria from the DAWN and DEFUSE-3 trials or in a few cases, an ASPECTS score <6. The results of this survey of experienced vascular neurologists and neurointerventionalists reinforces the disparity of approaches to imaging of transfer patients and those admitted directly to a thrombectomy center at various time points after stroke onset.

The benefits of thrombectomy in patients with LVO are obvious with a dramatic treatment effect in both the earlier and later time windows evaluated in the available clinical trials. Not surprisingly, the earlier time window trials appeared to show benefits in a broader range of patients than the narrowly selected patients in the 2 later time window patients. Symptomatic hemorrhagic side effects were not a concern in the earlier time window trials but may be an issue in patients treated beyond 6 to 8 hours based upon limited data from DAWN and DEFUSE-3. Even in the late time windows, this risk has to be weighed against the exceptionally poor outcomes in the control arm. Challenges remain for deciding about when to withhold thrombectomy in both the early and late time windows, that is, what ASPECTS score of ischemic core volume precludes a beneficial treatment effect at what age, with what comorbidities, and with what degree of collateral blood flow? Ongoing and planned clinical trials will hopefully answer these and other important questions, so that we can use this powerfully effective treatment that is resource intense and expensive as effectively and safely as possible.

Although there continues to be significant variation in imaging protocols and imaging-based selection criteria even among experts as demonstrated here, we feel that there will be greater degree of congruence with more data and a push toward more efficiency. Clearly, there is no best imaging protocol. However, given the importance of time is brain, every imaging protocol should be focused on efficient data acquisition and interpretation, as well as rapid decision-making. Of course, we need to exclude hemorrhage before intravenous tPA and determine the presence of a target (LVO) for thrombectomy. However, given the powerful effect and low complication rate of thrombectomy, the poor natural history of patients with LVO, we as a scientific community will have to think about which patients with LVO should not be offered treatment.

## Disclosures

Dr Fisher is compensated by the American Heart Association for serving as the Editor-in-Chief of Stroke. Dr Goyal has received compensation for consulting with Medtronic, Stryker, Microvention, and Cerenovus. He has a licensing agreement with GE Healthcare regarding Systems of Stroke Diagnosis. Medtronic provided an unrestricted research grant to the University of Calgary for the HERMES collaboration.

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KEY WORDS: Editorials ■ angiography ■ humans ■ stroke ■ thrombectomy

Stroke
Journal of the American Heart Association



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*Stroke*. published online June 26, 2018;
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628