# The Extended Treatment Window's Impact on Emergency Systems of Care for Acute Stroke

Joseph B. Miller, MD, MS, Laura Heitsch, MD, Tracy E. Madsen, MD, ScM, John Oostema, MD, Mat Reeves, BVSc, PhD, Christopher G. Zammit, MD, Noor Sabagha, MPH, Cemal Sozener, MD, MEng, Christopher Lewandowski, MD and Jon W. Schrock, MD

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## ABSTRACT

The window for acute ischemic stroke treatment was previously limited to 4.5 hours for intravenous tissue plasminogen activator and to 6 hours for thrombectomy. Recent studies using advanced imaging selection expand this window for select patients up to 24 hours from last known well. These studies directly affect emergency stroke management, including prehospital triage and emergency department (ED) management of suspected stroke patients. This narrative review summarizes the data expanding the treatment window for ischemic stroke to 24 hours and discusses these implications on stroke systems of care. It analyzes the implications on prehospital protocols to identify and transfer large-vessel occlusion stroke patients, on issues of distributive justice, and on ED management to provide advanced imaging and access to thrombectomy centers. The creation of high-performing systems of care to manage acute ischemic stroke patients requires academic emergency physician leadership attentive to the rapidly changing science of stroke care.

Acute ischemic stroke in the United States is the fifth leading cause of death and the leading cause of preventable disability and has an incidence of over 700,000 annual events.[1] The treatment of acute ischemic stroke changed dramatically following the publication of the National Institute of Neurological Disorders and Stroke (NINDS) trials in 1995,[2] which demonstrated improved outcomes for patients treated with intravenous tissue plasminogen activator (IV t-PA). Since then, national quality improvement efforts such as Get With The Guidelines - Stroke have sought to promote rapid stroke evaluation and IV t-PA delivery to appropriate patients.[3]

Patients with acute ischemic stroke and large-vessel occlusion (LVO) are at especially high risk of poor outcomes. They represent only one-third of all ischemic stroke cases, but LVO strokes are responsible for over 95% of acute ischemic stroke–related mortality and 60% of acute ischemic stroke–related death or permanent dependency.[4] Without emergent recanalization, 60% to 80% of LVO strokes result in death or permanent disability.[5,6] Landmark trials published in 2015 used clinical and imaging-based criteria to select LVO stroke patients for endovascular therapy and significantly changed the treatment landscape for acute ischemic

From the Department of Emergency Medicine, Henry Ford Hospital (JBM, NS, CL) and Wayne State University (JBM, CL), Detroit, MI; the Department of Emergency Medicine, Washington University School of Medicine (LH), St. Louis, MO; the Department of Emergency Medicine, Brown University School of Medicine (TEM), Providence, RI; the Department of Emergency Medicine (JO) and the Department of Epidemiology and Biostatistics (MR), Michigan State University College of Human Medicine, East Lansing, MI; the Departments of Emergency Medicine, Neurology, and Neurosurgery, University of Rochester Medical Center (CGZ), Rochester, NY; the Department of Emergency Medicine, University of Michigan (CS), Ann Arbor, MI; and the Department of Emergency Medicine, MetroHealth Medical Center, Case Western Reserve University (JWS), Cleveland, OH.
Received December 5, 2018; revision received January 14, 2019; accepted January 16, 2019.
The authors have no relevant financial information or potential conflicts to disclose.
Author contributions: JBM, LH, TM, and JWS conceived and designed this manuscript; all listed authors participated in synthesis of the literature and drafting of the manuscript; and JBM takes responsibility for the paper as a whole.
Supervising Editor: Peter Panagos, MD.
Address for correspondence and reprints: Joseph Miller, MD; e-mail: Jmiller6@hfhs.org.
ACADEMIC EMERGENCY MEDICINE 2019;26:744–751.


ISSN 1553-2712

doi: 10.1111/acem.13698

stroke.[7–12] These trials demonstrated endovascular therapy as a highly effective treatment for LVO stroke and revealed the potential for beneficial treatment beyond the 4.5-hour IV t-PA treatment window.[12]

Ongoing advancements in the imaging selection of stroke patients most likely to benefit from reperfusion therapies led to the conduct and recent publication of three trials in 2018 that are highly relevant to emergency care.[13–15] They shift the paradigm of acute ischemic stroke treatment from time-based to "tissue-based" treatment decisions. Tissue-based assessment determines salvageable brain tissue on advanced imaging rather than rigid treatment windows defined by time from last known well.[16] This paper summarizes these trials and analyzes their potential impact on stroke systems of care. We analyze the impact on prehospital stroke care, on relevant issues of distributive justice, and on emergency department (ED) management.

## THROMBECTOMY TRIALS EXPANDING TREATMENT UP TO 24 HOURS FROM SYMPTOM ONSET

The DAWN[13] and DEFUSE-3[14] trials were prospective studies that randomized late-presenting patients with anterior LVO stroke to endovascular thrombectomy plus standard medical therapy versus standard medical therapy alone (Table 1). Both studies enrolled patients with a last known well time > 6 hours prior to presentation (6–24 hours for DAWN and 6–16 hours for DEFUSE-3). These studies utilized advanced imaging protocols to ensure the presence of LVO without large areas of core infarct. The primary outcome was the proportion of patients with functional independence at 90 days, defined as a modified Rankin scale (mRS) score of 0 to 2. The DAWN trial also had a coprimary endpoint of the mean utility-weighted mRS, a patient-centered outcome using the mRS and a utility approach to quality of life.

In these trials, subjects had major neurologic deficits with small-volume ischemic core on imaging at the time of enrollment. The trials defined the ischemic core by measurements using computed tomography (CT) perfusion imaging and RAPID software (iSchemaView). In DAWN, patients had to have a mismatch between the volume of the ischemic core and clinical findings determined by the patient's NIHSS. In DEFUSE-3, patients had to have a ratio of ischemic tissue to infarct volume on perfusion imaging of 1.8 or greater.

Table 1
Comparing Recent Trials of Extended Treatment Windows for Acute Stroke Patients*

| | DAWN13 | DEFUSE-314 | WAKE-UP15 |
|---|---|---|---|
| Intervention vs. standard care | Thrombectomy | Thrombectomy | IV t-PA |
| Enrollment window (hr) | 6–24 | 6–16 | >4.5 |
| Time from randomization (hr), median (IQR) | 12.2 (10.2–16.3) | 10.9 (8.8–12.3) | 10.3 (8.1–12.0) |
| Age limit (years) | ≥18 | 18–90 | 18–80 |
| Mean (±SD) or median (IQR) | 69.4 (±14.1) | 70 (59–79) | 65.3 (±11.2) |
| Lower limit of baseline NIHSS | ≥10 | ≥6 | >0 |
| Baseline NIHSS, median (IQR) | 16 (10–20) | 17 (13–21) | 6 (4–9) |
| Preexisting disability limit (mRS) | ≤1 | ≤ 2 | ≤1 |
| Upper limit of infarct volume (mL) | <51 | <70 | NA |
| Volume of ischemic core (mL), median (IQR) | 7.6 (2.0–18.0) | 9.4 (2.3–25.6) | 2.0 (0.8–7.9) |
| Ratio of ischemic tissue to infarct core | Clinical mismatch† | ≥1.8 | NA |
| Functional independence at 90 days | | | |
| Intervention group vs. control | 49% vs. 13% | 45% vs. 17% | 53% vs. 42% |
| Number needed to treat (95% CI) | 3 (2–4) | 4 (3–7) | 9 (5–36) |
| Safety outcomes, intervention vs. control | | | |
| Death at 90 days | 19% vs. 18% | 14% vs. 26% | 4.1% vs. 1.2% |
| Parenchymal hematoma type 2 | 1.9% vs. 1.0% | 9% vs. 3% | 4.0% vs. 0.4% |

*Characteristics and results presented of treatment groups only, except where indicated. The enrollment window as measured from the last known normal time. Functional independence defined as a mRS of 0 to 2 in DAWN and DEFUSE-3 but 0 or 1 in WAKE-UP. Parenchymal hematoma type 2 is defined as an intracerebral hemorrhage involving more than 30% of the infarcted area with a substantial space-occupying effect or that is remote from the original infarcted area.
IQR = interquartile range; mRS = modified Rankin scale; NA = not applicable; NIHSS = National Institutes of Health Stroke Scale.
†Clinical mismatch categorized in three groups: A = age ≥ 80 years, NIHSS ≥ 10, infarct volume < 21 mL; B = age < 80 years, NIHSS ≥ 10, infarct volume < 31 mL; C = age < 80 years, NIHSS ≥ 20, infarct volume < 51 mL.

Both trials were stopped early when prespecified interim analyses demonstrated significant benefit in the thrombectomy arm. Significantly higher rates of vessel recanalization at 24 hours were seen in the treatment groups compared to the control groups (77% vs. 39% in DAWN, $p < 0.001$; 78% vs. 18% in DEFUSE-3, $p < 0.001$). Recanalization translated to improved functional outcomes between treatment and control groups. In DAWN, the mean score for the utility-weighted mRS at 90 days was significantly higher in the thrombectomy group compared to the control group (adjusted difference 2.0 points, 95% confidence interval [CI] = 1.1 to 3.0), indicating more favorable outcomes. In DEFUSE-3, endovascular treatment was associated with a favorable shift in the distribution of mRS at 90 days (odds ratio [OR] = 2.77, $p < 0.001$). Patients treated with thrombectomy had substantially higher rates of functional independence (mRS = 0–2) at 90 days, resulting in a very low number needed to treat for benefit in both studies (Table 1).

## EXPANDING IV t-PA TREATMENT PAST 4.5 HOURS

Both DAWN and DEFUSE-3 had substantial numbers of participants with "wake-up" strokes (63 and 53%, respectively) in the thrombectomy groups. Wake-up strokes are those in which a patient awakens with stroke symptoms, but whose last known normal time was before going to sleep. These patients have historically been excluded from IV t-PA treatment due to inability to determine the true time of onset for their stroke. Furthermore, many patients with wake-up strokes do not have an LVO. The recently published WAKE-UP[15] study was a randomized, double-blind controlled trial comparing IV t-PA versus placebo among ischemic stroke patients with unknown time of onset and stroke recognized > 4.5 hours prior to presentation. Patient eligibility required emergent magnetic resonance imaging (MRI) and abnormal signal on diffusion-weighted imaging (DWI) with no visible signal change on fluid-attenuated inversion recovery (FLAIR) imaging. Prior research demonstrated that this DWI-FLAIR mismatch indicates an onset time within the past 4 to 5 hours.[17] Major inclusion/exclusion criteria as well as characteristics of the IV t-PA group are summarized in Table 1.

The trial was stopped early due to cessation of funding with 503 of the planned 800 patients enrolled. Patients with favorable DWI-FLAIR mismatch that received IV t-PA were significantly more likely to have a favorable outcome, defined as a mRS score of 0 or 1 at 90 days (adjusted OR = 1.61, 95% CI = 1.09 to 2.36).[15] There was no significant difference in symptomatic intracranial hemorrhage, although there was a higher rate of the most severe form of radiologically classified hemorrhage, parenchymal hemorrhage Type 2, in the IV t-PA group (Table 1, $p = 0.03$).[18,19] There was also a nonsignificant trend toward higher mortality rates in the IV t-PA cohort (adjusted OR = 3.38, 95% CI = 0.92 to 12.52).

## THE EXPANDED TREATMENT WINDOW'S IMPACT ON PREHOSPITAL STROKE CARE

The trials discussed above expand the treatment window to select patients. To translate these findings into clinical practice necessitates change to existing methods of patient selection and triage. Here we discuss the prehospital implications in reengineering stroke systems of care. Thrombectomy is time-sensitive and is only available at a limited number of stroke centers.[20,21] Rapid identification and direct transport of LVO patients in the field to thrombectomy-capable hospitals has the potential to improve patient outcomes. To do so, however, requires accurate identification of patients with LVO stroke in the prehospital setting.

Despite derivation of more than 30 different stroke severity tools for this purpose, most have not been prospectively validated in the field, and diagnostic performance has been highly variable.[22,23] The most rigorously studied LVO prediction tools include the Cincinnati Prehospital Stroke Severity Scale (CP-SSS), the Los Angeles Motor Score (LAMS), and Rapid Arterial Occlusion Evaluation (RACE).[24–27] Based on prehospital data alone, sensitivities for these tools range from 38% to 76%, specificities range from 72% to 87%, and none demonstrate clear superiority.[22] Table 2 demonstrates the accuracy of the common decision aid tools based on pooled data from a recent meta-analysis.[22] The test characteristics of these tools vary substantially due to differences in the amount and type of data collected on neurologic symptoms. The LAMS tool, for instance, only collects data on three aspects of motor function, whereas the NIHSS collects 13 data points on sensory, motor, ocular, and executive function. Current evidence suggests that all scales are at risk of both under- and overtriage of

Table 2
Prehospital Clinical Decision Aids for Triaging Suspected LVO Stroke Patients[23–27]

| | NIHSS* | RACE | CP-SSS | LAMS |
|---|---|---|---|---|
| Items scored | 13 | 6 | 3 | 3 |
| Score threshold | ≥6 | ≥5 | ≥2 | ≥4 |
| Sensitivity for LVO, % (95% CI) | 80 (0.75–0.85) | 69 (0.46–0.85) | 56 (0.50–0.63) | 38 (0.08–0.81) |
| Specificity for LVO, % (95% CI) | 72 (0.70–0.74) | 81 (0.67–0.90) | 82 (0.73–0.89) | 87 (0.49–0.98) |
| Area under the curve* | 0.80 | 0.77 | 0.72 | 0.70 |

CP-SSS = Cincinnati Prehospital Stroke Severity Scale; LAMS = Los Angeles Motor Score; LVO = large-vessel occlusion; NIHSS = National Institute of Health Stroke Scale; RACE = Rapid Arterial Occlusion Evaluation.
*95% CI not available.

LVO stroke patients. It is not clear that clinical assessment-based prehospital assessments will adequately capture the heterogeneity of LVO stroke presentations.

To address the complex decision making around prehospital bypass decisions, the American Heart Association's Mission: Lifeline Stroke committee published a consensus prehospital triage algorithm for use by regional stroke systems.[28] According to this protocol, prehospital providers screen patients with suspected stroke using one of three stroke severity tools (CP-SSS, RACE, LAMS). They then transport patients with a positive LVO screen directly to a thrombectomy-capable center if the patient is within 6 hours of last known well and bypassing a closer ED would add less than 15 minutes to transport time. The real-world impact of such an algorithm is largely unknown, although a randomized controlled trial (RACECAT) using this strategy is ongoing.[29]

In light of the recent trials expanding the thrombectomy treatment window to 24 hours, the 6-hour limit in such protocols requires reexamination. Bypassing stroke-ready hospitals and primary stroke centers up to 24 hours after symptom onset may expedite therapy for those patients who meet thrombectomy criteria. Indeed, interhospital transfer is associated with onset-to-revascularization delays averaging more than 100 minutes.[30] However, such bypass protocols could also negatively impact care by placing patients farther from their families and overwhelming the stroke response systems of comprehensive stroke centers with patients who are not candidates for intervention.

Even if prehospital stroke assessment tools improve substantially in identifying LVO in the extended 6- to 24-hour time frame, many of these patients will ultimately not qualify for thrombectomy based on the selective imaging criteria in DAWN and DEFUSE-3.[31] Development of bypass protocols that address such challenges while still ensuring rapid access to thrombectomy for eligible patients is a major research need. In the interim, prehospital triage algorithms require the input of emergency physicians for local consideration of EMS capacity, transport distances, and hospital resources to design regional protocols that maximize access to thrombectomy for appropriate candidates while minimizing wasteful resource utilization.

## ISSUES OF DISTRIBUTIVE JUSTICE IN CHANGING STROKE SYSTEMS OF CARE TO EXPAND THE TREATMENT WINDOW

The ethics of distributive justice address the balance between benefits and burdens within a population.[32] When considering triage and management of potential LVO stroke patients, there exists a balance between providing the greatest benefit to these patients while limiting burdens to the remaining population of patients seeking emergency medical care at a single site or within a larger system. As noted, bypassing of closer hospitals for potential LVO patients can also strain patient families, consume prehospital resources, and overwhelm academic stroke centers with nonthrombectomy candidates.

The ethical conflicts arise between the utilitarian goal to do the greatest good for the greatest number and the principles of nonmaleficence and equal respect for all.[33] Triage decisions become challenging when a condition is life-threatening and a lifesaving resource is scarce, such as occurs in disaster situations. In the case of thrombectomy, the scarcity of the resource is rapidly changing. With 2011 data, 56% of people within the United States had access by ground to endovascular-capable hospitals within 60-minute transport time.[21] By air transport, this proportion increased to 85%. As health systems create referral patterns and increase their capacity to perform emergent thrombectomy, the scarcity of endovascular care will shrink. Likewise, the scarcity of emergent MRI may shrink and provide added treatment capacity for patients without LVO who present > 4.5 hours from last known well.

Thrombectomy for eligible LVO stroke patients is one of the most impactful, evidence-based emergency medical interventions. Hence, relative to many other emergent diagnoses and interventions, there should be a higher rate of tolerance for false positives in screening and for relocating resources from other sick patients. Such tolerance is dependent on the values communities hold and operational decisions by health systems.

## THE EXPANDED TREATMENT WINDOW'S IMPACT ON ED AND HOSPITAL STROKE READINESS

At the ED and hospital level, operational decisions largely fall within their stroke care designations. The Joint Commission began designating primary stroke centers (PSCs) in 2004. The PSC was required to demonstrate compliance with specific quality measures and demonstrate a minimum number of strokes that were treated with IV t-PA or thrombectomy.[34] Subsequently, The Joint Commission also began recognizing centers capable of providing more advanced stroke care, defined as comprehensive stroke centers (CSC).[35] Beyond PSC requirements, CSCs provide neurocritical care, 24/7 access to advanced imaging, endovascular procedure capability, and on-site neurosurgical providers.

Recently, The Joint Commission also began certifying thrombectomy-capable hospitals (TCHs).[36] These represented an intermediary between CSCs and PSCs and originally required physician-specific certification to perform acute stroke thrombectomy and minimum procedural volumes. Nevertheless, in September 2018, The Joint Commission suspended physician training and volume requirements for both CSC and TCH hospitals.[37] Interventional experts in acute stroke therapy raised concern over this change, noting that evidence to support good outcomes for LVO patients is lacking when thrombectomy is performed by low-volume hospitals.[38] Centers with higher volumes and ongoing quality improvement processes demonstrate faster door-to-treatment time for thrombectomy and excellent outcomes in prior trials.[39–41] While TCHs have the potential to lower times to treatment in geographic locations where CSCs are sparse, striking the right balance between access and adequate expertise in LVO management requires further investigation.

The advances in stroke therapy have created an imperative for EDs to establish protocols to identify acute ischemic stroke patients who might benefit from reperfusion therapies. This includes screening protocols for LVO for patients up to 24 hours past their last known well time. Many EDs have developed protocols for patients who present within 6 hours since last known well, but the results of DEFUSE-3 and DAWN broaden the challenge of screening many more patients up to 24 hours from onset of symptoms.[42] Some EDs have implemented broad screening protocols that include performance of CT angiography (CTA) in every code stroke patient.[43] Other systems perform CTA selectively, based on clinical criteria such as a LAMS score $\geq 4$ or NIHSS $\geq 6$.[44] Data indicate that use of a NIHSS $\geq 6$ to select patients for CTA has 80% sensitivity and 72% specificity for predicting LVO.[22]

In addition to expanding the pool of stroke patients who require screening for LVO, the results of DAWN and DEFUSE-3 have implications for the imaging techniques required. These trials used perfusion imaging to determine infarct size and perfusion mismatch with RAPID software.[13,14] While RAPID software performs automated calculation of the ischemia to infarct ratio on CT perfusion, it should be noted that such a calculation can be accomplished without proprietary software and that MRI with MRI perfusion is an alternative screening methods.[42] Figure 1 demonstrates CT perfusion images with RAPID software calculation in a patient with a LVO that stands to benefit from thrombectomy. The perfusion mismatch ratio is 7.9, indicating a significant volume of hypoperfused tissue relative to infarcted tissue. If perfusion imaging is not available, transfer to a facility that can perform appropriate imaging and thrombectomy should be considered. The American Heart Association guidelines endorse telemedicine with stroke teams to assist in the processes around advanced imaging and transfer criteria.[42]

Health systems are beginning to test protocols to optimally manage wake-up stroke patients. Many stroke patients with unknown onset outside the traditional 4.5-hour treatment window may be candidates for IV t-PA. Nevertheless, based on the WAKE-UP study protocol, determination of eligibility requires estimation of the diffusion-FLAIR mismatch on MRI. Fewer EDs have emergent MRI capacity compared to CTA and CT perfusion imaging. There is a need for further research to determine the real-world application of the WAKE-UP protocol and to determine if select wake-up patients benefit

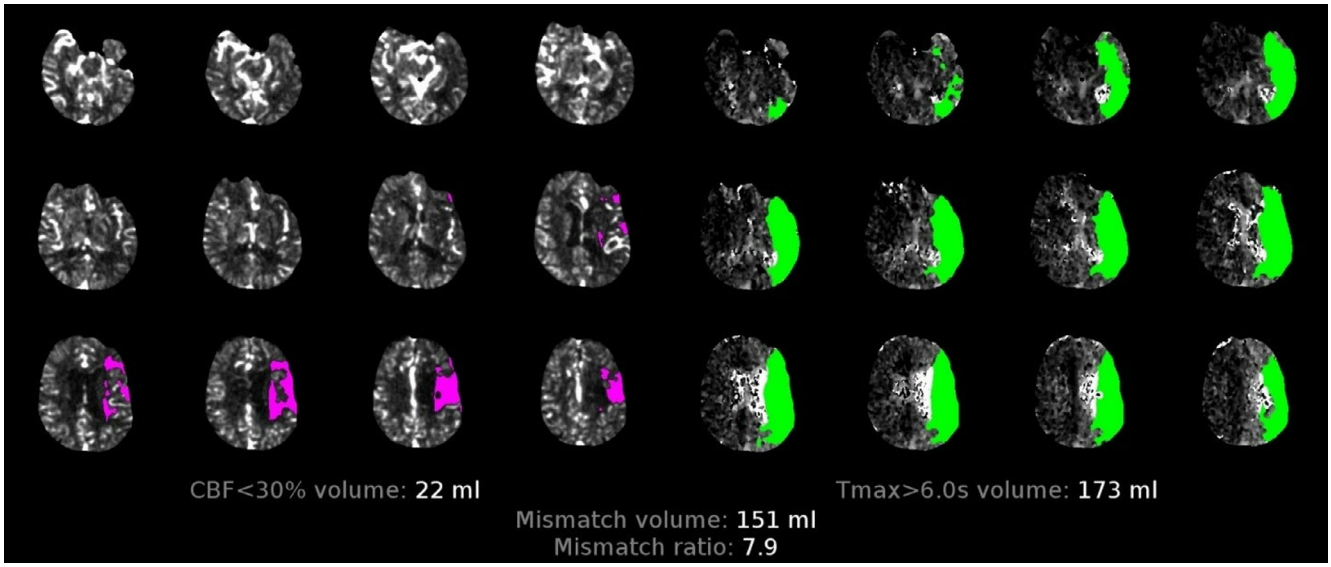


**Figure 1.** Example of computed tomography perfusion imaging showing a significant mismatch between early infarction (ischemic core) and hypoperfused brain tissue (ischemic tissue).

from transfer when emergent MRI is not available at a presenting ED.

The complex decision making involved in managing patients eligible for the time-sensitive interventions of IV t-PA and thrombectomy requires well-orchestrated systems of care. Development of clear protocols for EDs without thrombectomy capacity includes simplified decisions for advanced imaging, transfer decisions, and use of telemedicine. Many tertiary hospital systems have associations with smaller community sites that refer stroke patients to the hub hospital. Institutions not affiliated with a tertiary hospital should develop relationships with PSC and CSC hospital systems to develop protocols for the evaluation and transfer process for complex stroke patients who require higher levels of care.[45] Academic emergency physicians at the PSC and CSC sites can be instrumental in fostering these relationships and developing well-orchestrated systems of care.

## CONCLUSIONS

The expansion of the stroke treatment window based on advanced imaging criteria represents important advances in acute ischemic stroke therapy. Emergency physicians have significant leadership responsibilities in creating optimal systems of care. These responsibilities include leadership of medical control and prehospital protocols. They also include ED workflow, transport of select patients, and management within comprehensive stroke centers that have growing volumes of high-acuity stroke patients. Emergency physician guidance is critical in adapting the current science to improve systems of care and outcomes of acute ischemic stroke patients.

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