Four Evolving Strategies In The Emergent Treatment Of Acute Ischemic Stroke

Abstract

Stroke is the leading cause of long-term disability in the United States and is the fourth leading cause of death, affecting nearly 800,000 patients each year. The physical, emotional, and financial toll stroke inflicts on patients and their families cannot be overstated. At the forefront of acute stroke care, emergency clinicians are positioned to have a major impact on the quality of care that stroke patients receive. This issue outlines and reviews the literature on 4 evolving strategies reflecting developing advancements in the care of acute ischemic stroke and their potential to impact patients in the emergency department setting: (1) the expanding window for intravenous rt-PA, (2) the use of multimodal computed tomographic scanning in emergent diagnostic imaging, (3) endovascular therapies for stroke, and (4) stroke systems of care. Whether practicing in a tertiary care environment or in a remote emergency department, emergency clinicians will benefit from familiarizing themselves with these advancements and should consider how these new approaches might influence their management of patients with acute ischemic stroke.

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Case Presentations

A 64-year-old male presents to the ED with the acute onset of profound right-sided motor weakness and expressive aphasia. The patient has no headache, no history of trauma, and no other problems upon presentation. His only chronic medical problem is hypertension that is well controlled on his medications. His wife witnessed the onset of his symptoms while they were eating dinner 3.5 hours prior to arrival. He has normal vital signs, and a stat CT scan of the head is normal as are his laboratory studies. His deficits have persisted throughout his expedited workup and he is now 4 hours into an acute ischemic stroke (an hour beyond the FDA-approved treatment window for intravenous rt-PA), with a calculated NIHSS score of 16. What emergent treatment options, if any, do you have for this patient?

A 56-year-old male presents to the ED with a dense right-sided hemiparesis along with global aphasia and a leftward gaze deviation. He appears anxious, but otherwise he is in no acute distress and has normal vital signs. He was last seen normal approximately 9 hours ago, as he and his wife were going to bed. Upon awakening in the morning, he exhibited symptoms and was rushed to your hospital. His significant neurologic deficits persist, and his head CT shows only a hyperdense MCA sign on the left. What further diagnostic and therapeutic measures can be utilized to manage this patient's severe ischemic stroke?

A 72-year-old female presents to your ED with a severe left-sided hemiparesis, rightward gaze deviation, and hemineglect. She is a highly functioning lady and very active in her community. She had originally presented to an outside clinic and was then transferred to your ED. Her witnessed onset of symptoms occurred 6.5 hours prior to arrival, and her workup is negative other than a slight loss of grey-white differentiation in her right middle cerebral artery distribution on noncontrasted head CT. What therapeutic options might you employ to best emergently manage this woman's condition?

Introduction

Stroke is the fourth leading cause of death in the United States and the leading cause of long-term disability in adults.[1] Every year in the United States, approximately 795,000 individuals experience a new or a recurrent stroke.[2] Of these episodes, 77% (610,000) are initial attacks; 23% (185,000) are recurrent attacks. The risk of stroke is higher in men than in women, in blacks than in whites, and in older than in younger individuals. Stroke imparts a tremendous medical, emotional, and fiscal burden to society; annual costs for stroke care in the United States alone exceed $73 billion.[1] Clearly, improvements in early stroke care may reduce not only the morbidity and mortality of this devastating disease but also the significant financial cost.

Strokes may be classified as ischemic (87%), hemorrhagic (10%), or subarachnoid hemorrhage (3%). The distinction between these stroke subtypes is paramount, given the distinctly different diagnostic imaging modalities, treatment paradigms, and preventative measures used in their management. The important role played by emergency clinicians in the care of acute ischemic stroke cannot be overemphasized. Because they are always on the front lines of acute illness, emergency clinicians serve a critical role in the appropriate triage, workup, management, and disposition of acute stroke patients. Without the expertise and skill of emergency medicine providers, patients affected by stroke have little hope of receiving an expedited workup, much less the rapid and appropriate treatment decision that offers their best hope for neurological recovery.

Recent years have seen an explosion of advancements in the care of acute ischemic stroke patients. This article reviews 4 of the major evolving key elements that are changing the emergent management of acute ischemic stroke and are forming the basis of emergent stroke care for the future. Sections include:

Whether practicing in a major tertiary care center or in a remote emergency department (ED) setting, emergency clinicians must be familiar with advances in stroke care and how to best apply these advances to their practice setting.

There continue to be many controversies related to acute stroke care, and the authors recognize that there is significant regional and local variation in practice. Many considerations must be taken into account when tailoring a management strategy for the individual patient. The authors recommend that every hospital proactively develop protocols that address likely scenarios and thus maximize the delivery of care and minimize liability.

Abbreviations

A list of abbreviations can be found on page 28.

Review Of The Literature

The literature was searched using Ovid MEDLINE® and PubMed from 1990 to present. Areas of focus and key words included *acute ischemic stroke, computed tomographic angiography, computed tomographic perfusion, multimodal computed tomogra-*

phy, interventional stroke, endovascular stroke, stroke centers, organized stroke care, primary stroke centers, comprehensive stroke centers, healthcare systems, acute stroke with mechanical thrombectomy and *intra-arterial thrombolysis.* The studies were limited to humans. No language restrictions were applied. All study designs were included. This broad search yielded thousands of references, of which hundreds were reviewed. Only the most relevant references are provided with this manuscript.

Pathophysiology

Ischemic strokes consist of thrombotic strokes (approximately 60% of ischemic strokes), caused by in situ cerebrocervical artery occlusions usually secondary to atherosclerotic lesions, and embolic strokes (approximately 40% of ischemic strokes), caused by obstructive emboli from proximal vessel or cardiac sources.[3] Ischemic strokes result from the acute interruption of arterial blood flow to a dependent area of brain parenchyma. Once an arterial occlusion has occurred, a heterogeneous area of hypoperfused tissue is created. A central zone of ischemic tissue known as *the core* is completely deprived of critical oxygen and glucose delivery, and irreversible neuronal injury begins within minutes. Surrounding the core are areas of markedly decreased perfusion where "stunned" brain parenchyma receives a diminished blood supply from cerebral collateral vessels and potentially from residual arterial flow. This area, known as the *ischemic penumbra,* is potentially salvageable if significant arterial flow can be quickly restored, and thus it is the therapeutic target of reperfusion stroke therapies. Importantly, not all ischemic strokes are equal at the pathophysiologic level. Large vessel occlusions generally result in more severe strokes and poorer outcomes, and they can be more resistant to the re-establishment of blood flow than smaller vessel occlusions. With the advent of advanced neuroimaging, large vessel occlusions are readily identified and physiological differences between core and penumbral tissues may be elucidated, potentially altering reperfusion strategies. These topics will be more widely discussed in the sections that follow, as will their potential impact on the future of the emergent management of acute ischemic stroke.

Section I: The Expanding Window Of Opportunity In Acute Stroke: The Extended Window For Intravenous rt-PA Use

If left untreated, acute ischemic stroke may produce irreversible neuronal injury within minutes to a few hours, resulting in potentially devastating clinical outcomes. Prior to the study of fibrinolytic therapy for reperfusion, interventions to prevent these unfortunate outcomes were few, if any. Despite the fairly thorough understanding gained from animal models and the clinical observation of stroke patients of how quickly irreversible injury is produced by cerebral ischemia, many in the field were surprised by the clear and robust time-dependence of outcomes with reperfusion. Recent years have seen an intense focus on reducing delay from the time of symptom onset to hospital arrival as well as on minimizing intrahospital roadblocks, with many encouraging results. Along with continued efforts to maximize the efficiency of emergent stroke care, current research is also determining whether emergency clinicians can consider reperfusion strategies in patients who arrive later than the current United States Food and Drug Administration (FDA)-approved time windows dictate. This section addresses one of these approaches: the rapidly expanding utilization of intravenous (IV) recombinant tissue plasminogen activator (rt-PA) beyond the FDA-approved 3-hour window, along with discussion of the literature that supports this increasingly popular practice in the emergent treatment of acute ischemic stroke.

Extending The Time Window

The original National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial set a very high bar for healthcare providers treating patients with acute ischemic stroke: the initiation of fibrinolytic therapy within 3 hours from symptom onset.[4] This benchmark was consistently met in the NINDS trial through the dedication of the investigators, but generalization of the NINDS trial approach proved challenging in the years following the FDA approval of rt-PA in 1996. Numerous interventions, both past and present, were designed to increase the number of patients eligible for fibrinolytic therapy by reducing delays in the ischemic stroke pathway. In hopes of increasing the number of patients who arrive within 3 hours from symptom onset, a number of initiatives have been launched, including: (1) public awareness campaigns on the recognition of stroke and activation of emergency medical services (EMS), (2) increased EMS awareness of the signs and symptoms of stroke and the importance of rapid transport, and (3) EMS triage to the most appropriate stroke hospitals. In addition, much effort remains focused on improving inhospital systems to streamline the care of acute stroke patients into the optimal scenario with emphasis on decreasing door-to-imaging studies, laboratory studies, and, ultimately, door-to-needle times.[5,6] Along with these efforts, attention has been given to investigating the safety and benefit of extending the 3-hour window for IV fibrinolysis.[7]

Shortly after IV rt-PA was approved by the FDA in 1996, strategic initiatives were launched to investigate fibrinolytic options in patients who present beyond the 3-hour window. Physiologic imaging techniques using multimodal magnetic resonance imaging (MRI) and computed tomography (CT) attempt to identify salvageable penumbral brain parenchyma that might benefit from reperfusion strategies.[8] As detailed in Section II **(see page 6),** these modalities do not depend upon a temporal clock for the identification of potentially salvageable tissue for patient selection, but, rather, rely on a theoretically more accurate physiologic measure unique to each patient. This approach is promising, but it is still under investigation and is limited in its availability to more comprehensive stroke centers. Another approach, also based, in part, on individual patient physiology, is to identify a subset of ischemic stroke patients who may have a longer threshold for enduring ischemia and have potentially salvageable penumbral tissue beyond the 3-hour time window. Based on over a decade of data, it is known that patient characteristics help provide insight into overall outcome prognosis and response to fibrinolytic therapy.[9,10] For example, regardless of fibrinolytic therapy, worse outcomes are associated with patients who have advanced age, greater stroke severity by the National Institutes of Health Stroke Scale (NIHSS) score (available at http://nihstrokescale.org), early ischemic changes on baseline CT, elevated blood pressure on arrival, and a history of diabetes.[11-14] Data from several trials and registries suggest risk of symptomatic hemorrhage after IV rt-PA is associated with severity of neurological deficits on arrival, elevated baseline blood glucose, and early ischemic changes (especially early hypodensity) on baseline CT.[15,16] Other clinical and demographic features reportedly associated with increased risk of hemorrhage include advanced age, elevated systolic blood pressure on arrival, atrial fibrillation, and treatment with aspirin before fibrinolysis, but these are not as well established.[14-17] Recently, several groups have created prediction models to estimate prognosis after IV rt-PA administration.[9] The DRAGON score, validated at one large hospital in Helsinki, Finland, incorporates the presence of a hyper**d**ense middle cerebral artery, prestroke modified **R**ankin Scale score, **a**ge, baseline **g**lucose, **o**nset-to-treatment time, and baseline **n**eurologic deficit measured by the NIHSS score in a prognostic model that produced reasonable discrimination.[9]

This group of patients has similar issues even with reperfusion, but the overall benefit from fibrinolytic therapy remains when treatment occurs within the 3-hour window. Using the knowledge of how certain physiologic features influence outcomes may provide guidance for selecting treatments beyond current therapeutic time windows.

Early Thrombolytic Studies: ECASS I, ECASS II, ATLANTIS

Many of the early fibrinolytic studies that investigated the later time windows had similar inclusion criteria as the original NINDS rt-PA trial and did not use physiologic or imaging-based selection for inclusion into the study groups. Most of the studies utilized protocols that were very similar to the NINDS trial protocol, with the exception of rt-PA dosing, CT criteria, and specific time window. **(See Table 1.)** While the initial extended-window trials failed to demonstrate an overall proven clinical benefit, continued protocol modifications and patient selection refinement has led to later successful trials.

The early fibrinolysis trials – the European Cooperative Acute Stroke Study (ECASS) I and II – were very similar to the NINDS trial in design, with the exception of a higher dose of IV rt-PA used in ECASS I as well as the recruitment of patients out to 6 hours from symptom onset.[18,19] ECASS I failed to show a statistically significant difference in primary outcome (improved modified Rankin Scale [mRS] score or Barthel Index at 3 months), but it provided major insights for future trials. Had the NINDS global outcome statistic been used in ECASS I, the IV rt-PA group would have had a statistically significant increased rate of favorable outcome (odds ratio [OR] 1.5, 95% confidence interval [CI], 1.1-2.0). Additionally, the ECASS I trial reinforced the knowledge that patients with more severe strokes, older patients, and patients with early ischemic changes on baseline CT had worse outcomes, largely due to higher rates of intracranial hemorrhage. ECASS II utilized a similar protocol as used in ECASS I except the IV rt-PA dose was lowered to 0.9 mg/kg. Patients were stratified by 2 time epochs: 0 to 3 hours from symptom onset and 3 to 6 hours from symptom onset. The majority of patients were recruited in the 3- to 6-hour window (642 of the 800 total patients). The overall 3.7% absolute increase in improved outcomes (mRS score 0-1 at 3 months) in the IV rt-PA arm compared to the placebo arm was not statistically different ($P = 0.277$). A similar nonsignificant difference was found in patients enrolled in the 3- to 6-hour arm (40.2% vs 36.9%, $P = 0.42$). A post hoc analysis using a favorable outcome definition of mRS score 0 to 2 produced an 8.3% absolute difference in favor of IV rt-PA ($P = 0.024$). Mortality rates were comparable, even with rates of symptomatic intracerebral hemorrhage being significantly higher in the IV rt-PA arm. The lower rates of death in ECASS II and overall better outcomes compared to ECASS I were likely due, in part, to the fact that patients with less-severe strokes were enrolled in ECASS II.

Published in 1999, the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study was, again, similar to the NINDS trial in that it originally included patients from 0 to 6 hours from symptom onset, but it was

later modified to study patients specifically at 3 to 5 hours from onset (ATLANTIS B).[20] The primary outcome measure, a 3-month NIHSS score of 0 or 1 in ATLANTIS B, was not statistically significant between IV rt-PA and placebo (34% vs 32%, respectively). As seen in other trials, rates of symptomatic intracerebral hemorrhage (sICH) were higher with IV rt-PA (7% vs 1.1%, $P < 0.001$), but 3-month mortality was not statistically different (11.0% vs 6.9%, $P = 0.09$) with IV rt-PA. The relatively low mortality rates in both treatment and placebo arms may have been attributable to the less-severe strokes in patients in ATLANTIS as compared to the NINDS trial (median NIHSS score 10 vs 14, respectively). Lessons deduced from the experiences of ECASS I, ECASS II, and ATLANTIS helped design the next iteration of extended-window studies.[21-23]

Later Thrombolytic Studies: ECASS III, SITS-MOST, IST-3

As a requirement for the provisional approval of IV rt-PA use in Europe, the European Medicines Agency (EMA) required that an observational safety study be conducted. The study was called the Safe Implementation of Thrombolysis in Stroke – Monitoring Study (SITS-MOST). Additionally, EMA required a randomized, extended-time-window study to be conducted,

ECASS III, initially enrolling patients within 3 to 4 hours from symptom onset and later extending out to 4.5 hours.[24] ECASS III, again, used many of the same protocol elements as in prior thrombolysis studies, but based on the data from prior trials regarding favorable response to fibrinolytics beyond 3 hours, patients with high stroke severity (NIHSS score > 25), with extreme age (> 80 years), with a combination of prior stroke and diabetes, and on any anticoagulant therapy regardless of international normalized ratio (INR) were excluded. These criteria were deliberately selected to maximize the chances of favorable response based on a retrospective analysis of the SITS database that indicated minimal chance of improvement in these subgroups. The ECASS III trial enrolled 821 patients, with a median stroke severity of 9 and 10 in the treatment and placebo arms, respectively. The primary outcome measure, 3-month mRS score 0 to 1, occurred in 52.4% of the IV rt-PA arm compared to 45.2% in the placebo arm ($P = 0.04$) and remained statistically significant after adjustments for initial stroke severity and time from symptom onset to treatment. Not unexpectedly, sICH by NINDS definition was more frequent in the treatment arm compared to the placebo (7.9% vs 3.5%), but overall 3-month mortality was not significantly different (treatment 7.7% vs placebo 8.4%).

Table 1. Trials Of Extended Windows For Intravenous rt-PA

Study	Year Published	rt-PA Dose (mg/kg)	Time Window (hr)	Upper Age Limit (yr)	mRS 0-1 at 90 Days (%) in Treatment vs Placebo Groups	sICH Rate* (%) in Treatment vs Placebo Groups	90-Day Mortality (%) in Treatment vs Placebo Groups
ECASS I	1995	1.1	0-6	80	35.7 vs 29.3	6.3 vs 2.4#	22.0 vs 15.8
NINDS	1995	0.9	0-3	None	39 vs 26	6.4 vs 0.6	17.0 vs 21.0
ECASS II	1998	0.9	0-6	80	40.2 vs 36.9	8.3 vs 0.6	9.5 vs 11.3
ATLANTIS B	1999	0.9	3-5	80	42 vs 40	7.0 vs 1.1	11.0 vs 6.9
Pooled data	2004	0.9 and 1.1	0-6	None	0-90: 41 vs 29 91-180: 43 vs 30 181-270: 37 vs 33 271-360: 37 vs 36	5.9 vs 1.1	
ECASS III	2008	0.9	3-4.5	80	52 vs 45	7.9 vs 3.5	6.7 vs 8.2
SITS-ISTR^	2008	0.9	3-4.5	80	39 vs NA	1.6 vs NA	12.7 vs NA
IST-3	2012	0.9	0-6	None	37 vs 35+	7 vs 1	27 vs 27

*sICH by NINDS definition

Mortality rates due to intracranial hemorrhage

^ A registry so no control arm involved

+ Oxford Handicap Score at 6 months

Abbreviations: ATLANTIS, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; ECASS, European Cooperative Acute Stroke Study; IST-3, Third International Stroke Trial; mRS, modified Rankin Scale; NA, not available; NINDS, National Institute of Neurological Disorders and Stroke; rt-PA, recombinant tissue plasminogen activator; sICH, symptomatic intracerebral hemorrhage; SITS-ISTR, Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry.

Three concerns were expressed regarding the trial: (1) there was a greater incidence of prior stroke in the placebo (7.7% vs 14.1%, $P = 0.003$), (2) the study excluded patients with severe strokes (NIHSS score > 25), and (3) the study protocol was changed during the trial. Despite these issues, those heavily involved in the treatment of acute ischemic stroke were energized by these findings, as ECASS III represented the first positive randomized phase III fibrinolysis trial since the original NINDS trial. Also encouraging was the fact that the use of data from prior studies helped create a study design that seemed to increase the chances of a positive study and favorable clinical outcomes, lending momentum for the development of future reperfusion research strategies. Importantly, ECASS III authors and many others commented that while the study was positive, the mantra *time is brain* still holds true: the earlier that treatment can be initiated, the greater the patient's chance for a good clinical outcome.[25]

Utilizing data from extended window fibrinolytic trials in a meta-analysis, Lansberg et al confirmed the benefit of IV rt-PA treatment within 3 to 4.5 hours from symptom onset over placebo by various outcome measures while maintaining comparable 4-month mortality rates.[26] Additionally, an analysis of patient outcomes included in the Safe Implementation of Treatments in Stroke - International Stroke Thrombolysis Registry (SITS-ISTR) demonstrated that the group of patients treated from 3 to 4.5 hours from symptom onset compared to those treated in under 3 hours demonstrated comparable mortality and sICH rates.[14] Additionally, outcome measures were also comparable between these groups (3-month mRS score 0-1, 41% vs 40% for 3-4.5-hour and < 3-hour windows), further confirming the benefit of IV rt-PA in the extended 4.5-hour therapeutic window.

The most recent study of fibrinolysis in acute stroke, the Third International Stroke Trial (IST-3), was conducted in over 12 countries and enrolled 3035 patients. This study of a 0- to 6-hour fibrinolysis window confirmed the benefit of IV rt-PA seen in previous studies, but the effect, given the longer time window, was more modest than in the NINDS Trial (37% vs 35%, mRS score 0-1 at 6 months).[27] Incorporating these data into a large meta-analysis of IV rt-PA administered within 6 hours from symptom onset, Wardlaw and colleagues again confirmed the benefit of fibrinolytic treatment, and, importantly, the association of improved outcomes with earlier treatment.[28] Additionally, the authors were able to demonstrate that elderly patients (> 80 years of age) achieved similar benefit as younger patients. With the cumulative data to date, fibrinolytic therapy, appropriately administered, improves clinical outcomes. As the time from symptom onset increases, the potential for benefit decreases, so every effort should be made to reduce pretreatment delays. Data for patients who are beyond 3 hours and elderly (> 80 years of age), with severe strokes (NIHSS score > 25), with prior stroke and diabetes, or who are taking oral anticoagulants are less robust, and potential use of fibrinolysis should be discussed with the patient and family prior to administration.

Summary: The Extended Window For Intravenous rt-PA Use

The new extended fibrinolysis window represents a major advance in the treatment of patients with acute ischemic stroke. With the expansion of the time window to include those presenting within 4.5 hours of symptom onset, the subgroup of patients who were presenting in this later therapeutic window that was previously excluded from receiving critical reperfusion therapy may now be eligible for emergent IV thrombolytic treatment for acute ischemic stroke. Ongoing studies will continue to refine which patients are most likely to benefit from fibrinolytic therapy in this extended 4.5-hour window as well as whether those patients excluded from ECASS III may also benefit from the expanded time window. Two important take-home messages are also found in these studies. First, in all studies to date, protocol violations are associated with increased rates of symptomatic hemorrhage and worse outcomes; thus, regardless of the protocol used and the time window considered, strict adherence to pre- and post-IV rt-PA protocols is crucial.[19] Second, emphasis that *time is brain* remains. The earlier treatment is initiated, the greater the opportunity for the stroke patient to experience a positive clinical outcome. Future efforts should focus persistently on improving efficiency in the emergent treatment of acute ischemic stroke and on the continued building of fortified stroke systems of care **(see Section IV, page 16),** which serve to reduce symptom-onset-to-needle times and provide ever-increasing optimism in the care of stroke patients.

Section II: The Use Of Multimodal Computed Tomography In Acute Stroke Imaging

The conventional ED acute stroke protocol calls for rapid patient assessment, determination of serum glucose, and expedited emergent neuroimaging. Well-established by the NINDS Study Group and multiple subsequent recommendations by the American Stroke Association, the initial imaging modality of choice since the advent of thrombolytic therapy for stroke has been an immediate noncontrasted CT scan of the head.[29,30] While the primary function of noncontrasted head CT is to make the critical distinction between acute hemorrhagic and acute ischemic stroke, early indicators of cerebral ischemia such as loss of the insular ribbon[31] or obscuration of the lentiform nucleus[32] may also be observed. These

early ischemic changes may appear in up to one-third of patients within 3 hours of stroke symptom onset but may also indicate that the index stroke time of onset is earlier than initially thought. Furthermore, while early ischemic changes on CT scan correlate with stroke severity, these early findings are not independently associated with adverse outcomes in patients treated with IV rt-PA.[33] Another early finding on noncontrasted CT is the hyperdense artery sign, which is indicative of an acute thrombus within a cerebral arterial vessel leading to acute ischemic stroke.[34,35] Though the detection of these early CT findings may be helpful in identifying early acute ischemic stroke, none are sensitive and may be quite subtle even when present.[36]

Recent years have seen the emergence of newer technologies that enable medical professionals to move beyond noncontrasted head CT and its limitations in the evaluation of early cerebral ischemia through the incorporation of multimodal CT scanning into their practice. These advanced imaging studies provide a means to augment the emergency clinician's ability to identify at-risk ischemic tissue and may aid with critical triage decisions in the care of acute stroke patients.

Description And Potential Clinical Implications Of Multimodal Computed Tomographic Imaging

As outlined earlier, noncontrasted CT scanning is extremely valuable in rapidly identifying intracranial hemorrhage in the acute stroke patient, serving as a critical fork in the clinical pathway of emergent stroke treatment. Nonetheless, the study is generally limited in its ability to reliably identify acute cerebrovascular occlusions as well as freshly ischemic or infarcted brain tissue. Multimodal CT scanning offers a more comprehensive approach to emergent neuroimaging in the acute stroke patient and provides important information on the "4 Ps" of acute stroke imaging: **P**arenchyma (brain), **P**ipes (vasculature), **P**erfusion (blood flow), and **P**enumbra (at-risk tissue).[37] This approach offers a sequence of studies that can be rapidly obtained and analyzed, consisting of noncontrasted head CT, CT angiography (CTA) of the head and neck, and perfusion CT (CTP),[38] and greatly enhances the sensitivity of emergent CT neuroimaging for acute ischemic processes.[39] With the technological advancements of multidetector-row helical CT scanners, these studies can be obtained in minutes and produce high-quality images for clinical use. Given the widespread availability of CT scanners in EDs nationwide, emergency clinicians may employ these advanced imaging modalities and utilize them to more effectively evaluate acute stroke patients by adding a new dimension of radiological insight into their condition.

CTA of the head and neck offers valuable information in the treatment of acute ischemic stroke and can image the entire cerebrovascular tree and its major contributing vessels in a matter of seconds.[40,41] With the use of CTA, large vessel occlusions are rapidly demonstrated, potentially guiding emergent therapy by identifying a clot burden that may theoretically be more susceptible to endovascular intervention than IV thrombolytics alone. Conversely, the lack of a large vessel occlusion on CTA may steer clinicians away from performing invasive endovascular interventions that are unlikely to provide benefit to the patient. In addition, arterial dissections may be elucidated on CTA and elaborate the cause of ischemic stroke, further guiding potential therapeutic interventions. Early identification of large cerebrovascular occlusions may be of particular benefit to patients seen in EDs that lack endovascular interventional resources. When a large vessel occlusion is identified, interventional centers may be contacted with concrete information regarding the site and extent of vascular obstruction. This critical information may lead to enhanced coordination of care, allowing for "drip and ship" models of therapy, where indicated, as well as the potential for facilitation of direct patient transfer to the procedural suite for emergent reperfusion therapy.

CTP studies offer the emergency clinician remarkable insight into the current tissue state of the brain at the capillary level and help differentiate infarcted parenchyma from at-risk potentially salvageable penumbral tissues.[42] Though the accepted gold-standard assessment of underperfused brain tissues has been perfusion- and diffusion-weighted MRI studies, the availability of these studies is limited in most ED settings. However, comparable perfusion assessments of at-risk tissues may be achieved with CTP, equipping emergency clinicians with a powerful and rapid appraisal of the physiologic state of brain parenchyma.[43,44] In essence, this is accomplished through the generation of quantitative maps of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT), and the use of this information to produce color-coded summary maps of the hemodynamic status of brain parenchyma.[45,46] MTT is the average time taken for blood to pass through a given zone of brain parenchyma and may be mathematically represented by dividing cerebral blood volume by cerebral blood flow (MTT = CBV ÷ CBF), with CBV being measured in mL of blood / 100 grams of brain tissue and CBF measured in mL of blood / 100 grams of brain tissue / minute.

In the setting of ischemic stroke, tissue is traditionally categorized into the *ischemic core* (irreversibly damaged brain tissue) and the *ischemic penumbra* (hypoperfused tissue, potentially salvageable with

successful reperfusion). With the advances of CT perfusion technology, these tissues are radiographically distinguishable, as the infarct core features prolonged MTT with dramatically decreased CBV and CBF, while the ischemic penumbra typically demonstrates prolonged MTT with decreased CBF and variable CBV.[47] Because of these physiologic differences at the capillary level and the ability to differentiate them with CTP, emergency clinicians may enjoy the ability to gather real-time hemodynamic information determining the state of brain parenchyma in the acute stroke patient and use this information to help guide critical emergent treatment decisions. Importantly, however, the evidence, to date, continues to demonstrate that improved clinical outcomes in acute ischemic stroke depend heavily on the rapidity of treatment (door-to-needle); thus, the acquisition of these imaging studies should never delay emergent therapeutic interventions when they are clearly indicated.

Evolving Imaging Strategies: A New Acute Stroke Treatment Paradigm?

Along with traditional ED acute stroke diagnostic protocols, the strict adherence to therapeutic time windows has been a constant in the expanding effort to provide emergent IV thrombolytic and endovascular interventions to appropriately selected patients. With the emergence of the technologies discussed above, a new paradigm in the emergent treatment of acute stroke is moving to the forefront in the management of the acute ischemic stroke patient. As has been suggested, the motto "time is brain" may be indeed shifting to "physiology is brain."[48] The importance of this strategic shift is underscored by the fact that such a small percentage of patients afflicted with acute ischemic stroke actually receive emergent reperfusion therapy.[49] Most commonly, patients are excluded due to their presentation beyond firm, well-established therapeutic time windows; however, current literature suggests that there may be salvageable ischemic penumbra well beyond the close of currently accepted time windows.[47,50] With the expansion of the use of multimodal CT in the emergent evaluation of stroke patients, there is great potential in identifying a larger number of patients who may benefit from emergent therapeutic interventions by identifying those patients who have salvageable penumbra even beyond traditional time windows of therapy. It is important to note, however, that, to date, there is no high-level evidence confirming the role of multimodal CT scanning in patient selection for appropriate therapies nor has a positive impact on clinical outcomes been demonstrated as a result of the use of these studies.[51,52]

One important group falling out of traditional therapeutic treatment windows includes those patients who suffer a "wake-up" stroke. These patients, because they were last seen normal prior to going to sleep not having exhibited the signs and symptoms of stroke within the window of therapy, have historically been excluded from emergent reperfusion therapy. For safety reasons, their stroke is presumed to have occurred outside of the window, and the means to radiologically prove otherwise have generally not been readily available in the ED setting. With the availability of multimodal CT, these patients can be emergently scanned, and if their imaging indicates significant penumbral tissues versus core infarct, the potential for treatment can be explored. In the images presented with this section, the case involved a patient with a wake-up stroke, having last been seen at his neurological baseline approximately 9 hours prior to his ED presentation. His CTA imaging revealed a proximal middle cerebral artery (MCA) occlusion **(see Figure 1),** and his CTP imaging demonstrated a very large penumbral area with only a few small areas of core infarction **(see Figures 2-5). Color versions of these images can be seen at www.ebmedicine.net/StrokeImages or in the PDF of this issue, available at www.ebmedicine.net.**
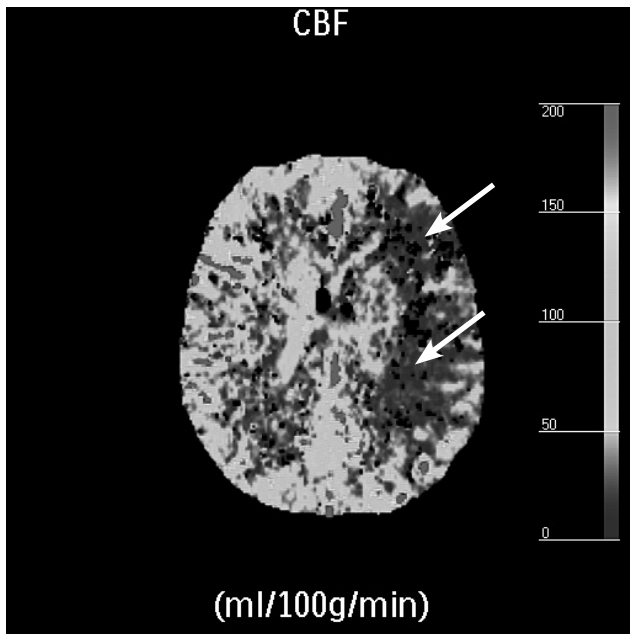
Figure 1. Middle Cerebral Artery Occlusion On CT Angiogram

CT angiogram demonstrates acute focal occlusion of the patient's left prebifurcation M1 segment in the middle cerebral artery (arrow).
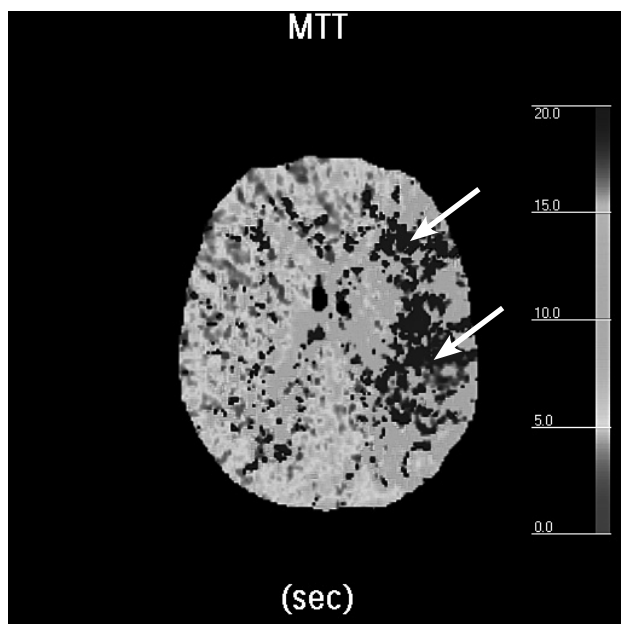Image used with permission of R. Jason Thurman, MD.

Figure 2. Cerebral Blood Flow On CT Perfusion Study

Cerebral blood flow on perfusion study demonstrates markedly diminished flow in the distribution of the left middle cerebral artery as compared to the right (large gray area pointed out by arrows, seen as blue in the color image [see online PDF]).
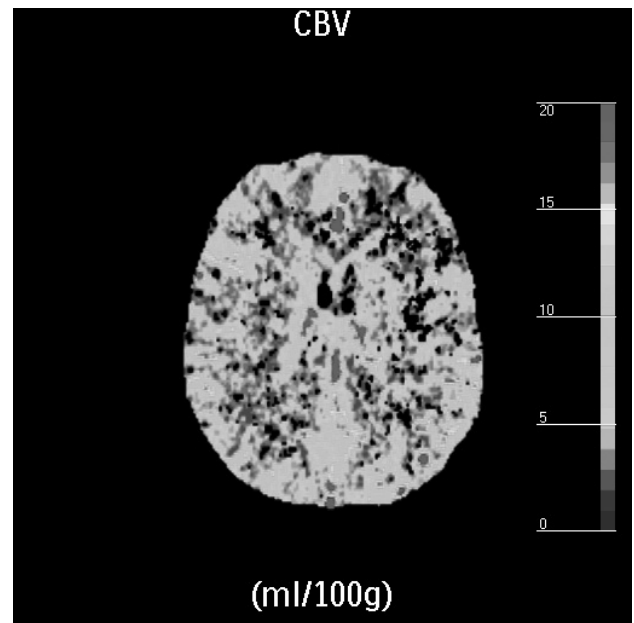Image used with permission of R. Jason Thurman, MD.

Figure 3. Cerebral Blood Volume On CT Perfusion Study

Cerebral blood volume on perfusion study demonstrates relatively preserved cerebral blood volume, reflected in the symmetry of the image, in the affected left middle cerebral artery distribution. (See color image in online PDF.)
Image used with permission of R. Jason Thurman, MD.

Figure 4. Mean Transit Time On CT Perfusion Study

Mean transit time on perfusion study demonstrates markedly increased transit time in the left middle cerebral artery distribution as compared to the right (includes the black areas pointed out by white arrows and seen in blue and green in the color image [see online PDF]).
Image used with permission of R. Jason Thurman, MD.

Figure 5. Perfusion Mapping On CT Perfusion Study
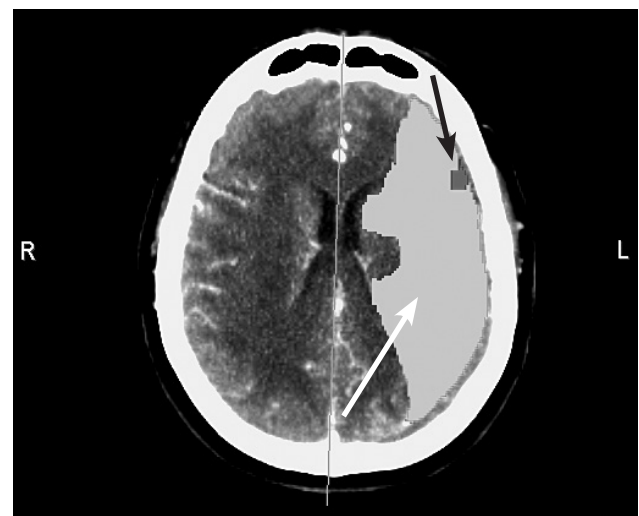
CT perfusion map demonstrates a large perfusion abnormality involving the entire left middle cerebral artery territory. The majority of the perfusion abnormality can be seen in the light gray shaded area (pointed out by the white arrow, and seen in green in the color image [see online PDF]) representing potentially salvageable ischemic penumbral tissues. A few core infarct areas (pointed out by black arrow, and seen as red in color image) are also seen. The large penumbral-to-core ratio prompted the decision to attempt mechanical clot removal.
Image used with permission of R. Jason Thurman, MD.

Because of these findings, this patient was taken for emergent endovascular treatment using the Merci Clot Retriever®. **(See Figure 6.)** His cerebral angiography studies are shown in **Figures 7 and 8**, with **Figure 7** demonstrating the vascular occlusion prior to intervention. His subsequent angiographic imaging, seen in **Figure 8**, reveals reperfusion of the ischemic MCA territory. This patient presented with an NIHSS score of 22 and left the hospital with no significant neurological deficit. This case illustrates one of the potential uses of multimodal CT for acute stroke patients and how its expanded utilization may play a role in furthering the deployment of emergent therapeutic options.

Whether inside or outside of current therapeutic time windows, multimodal CT scanning is likely to play an expanding role in selecting patients for appropriate interventions as well as in excluding patients from potential therapies that are unlikely to benefit the patient but may potentially cause harm. For example, if a large vessel occlusion is elucidated on CTA, the patient is unlikely to gain full restoration of blood flow with IV thrombolysis alone and may potentially be more optimally treated with additional rapid endovascular therapies.[53] In these cases, emergency clinicians can direct the care of the patient for consideration of an acute endovascular intervention much earlier than if further monitoring of clinical examination parameters are primarily used to make this determination. With CTP, if im-

ages indicate that no salvageable penumbra is present, emergent interventions may potentially cause more harm than good as patients may be exposed to the risks of thrombolytic therapy or endovascular interventions without the potential for meaningful neurological recovery.[52] However, if parameters indicate abnormal hemodynamics favorable for treatment, the emergency clinician may identify

Figure 6. Merci Clot Retriever® Deployment

Images taken in the angiography suite show the Merci Clot Retriever® in the left middle cerebral artery during clot removal attempt (arrow).
Image used with permission of R. Jason Thurman, MD.

Figure 7. Middle Cerebral Artery Occlusion On Cerebral Angiogram

Angiography demonstrates occlusion of the middle cerebral artery (arrow).
Image used with permission of R. Jason Thurman, MD.

Figure 8. Restoration Of Middle Cerebral Artery Flow On Cerebral Angiogram
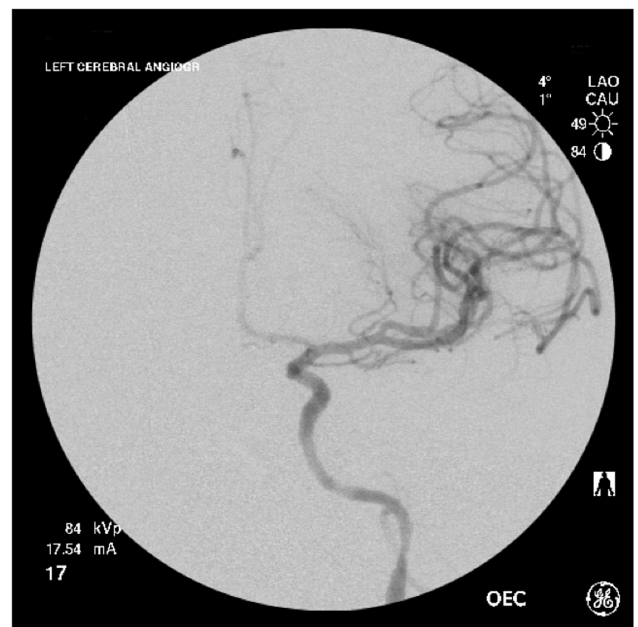
Angiography following clot extraction demonstrates complete recanalization of the middle cerebral artery with restoration of flow. The patient made a dramatic and near-complete neurological recovery.
Image used with permission of R. Jason Thurman, MD.

penumbral target tissues and select such patients for acute treatment modalities.[54,55] Although these triage strategies are becoming widespread in interventional centers, they have not been fully tested in a prospective clinical trial, and their true implications on clinical outcome remain unproven.

Finally, multimodal CT imaging can potentially be very helpful to emergency clinicians practicing in centers without the benefit of the presence of an acute stroke treatment team. As mentioned, multimodal CT images can be obtained rapidly and offer insight into the location of vessel occlusion as well as delineation of core infarct versus at-risk penumbral tissues. With this information in hand, emergency clinicians can provide a wealth of information to a receiving center and work in concert to initiate appropriate therapies as well as coordinate transfer of the patient to centers where state-of-the-art interventional capabilities are available. Whether these studies should be obtained prior to transfer versus opting for immediate transfer of patients with suspected acute ischemic stroke prior to imaging is an issue best left to each individual facility to determine in conjunction with its referral site in the spirit of optimal stroke management.

Potential Limitations To Multimodal Neuroimaging

Though multimodal neuroimaging offers many promising advantages, there are some limitations to consider. First, the studies are technically challenging and require well-synchronized timing of contrast bolusing and image acquisition for high-quality studies to be rendered.[38,40] There are many factors to be considered to achieve optimal imaging, including adequate venous access, contrast bolus timing, scanner parameters, injection parameters, physiological parameters affecting bolus geometry, as well as image processing pitfalls, but an in-depth discussion of these is beyond the scope of this article. It suffices here to say that well-organized imaging protocols and experienced CT technologists and radiologists are essential to consistency in imaging excellence.

In addition, the methods of defining significant perfusion mismatch parameters need further refinement, as earlier trials have included large volumes of benign oligemia (hypoperfused but potentially viable tissue) in their core-penumbra mismatch assessments.[56] Radiation exposure to the patient must also be considered as well as the potential consequences of the administration of iodinated high-density IV contrast. There is literature that suggests that contrast administration does not affect the clinical outcome of stroke patients.[57] There is also a published study that concludes that functional contrast-enhanced CT for the evaluation of ischemic stroke does not increase the risk of contrast-induced nephropathy. Nonetheless, subjects in this study consisted of patients with baseline median serum creatinines and glomerular filtration rates in the normal range.[58] Some sources, because of the risk of contrast-induced nephropathy, do advocate for the assessment of serum creatinine prior to contrast administration,[38,59] while others recommend that local guidelines be formulated and followed.[60] In general, review of the literature and informal discussions with multiple stroke center representatives leads to the conclusion that these "local guidelines" reflect that most centers do not routinely check serum creatinine prior to performing these studies because it is felt that the benefits of avoiding any time delay in studies and ultimate stroke therapy outweigh the potential risk of contrast-induced nephropathy in this patient population. One must also be aware of the additional costs associated with obtaining multimodal CT imaging and the financial impact this has on patients and their families, but, again, the potential benefits of the studies and their potential for impact on the clinical outcome for patients must also be weighed. Finally, as has been discussed, as of now, the use of multimodal CT scanning has not demonstrated a proven clinical benefit in a randomized controlled trial, making its true impact on clinical outcomes unknown. As more literature specifically addressing the issue of whether or not a clinical benefit results from selecting patients for treatment on the use of multimodal CT emerges, the most appropriate role of advanced imaging can be better defined. In the present, the authors of this work advocate for the judicious use of multimodal CT and, as with all emergent decisions, recommend that the risks and benefits for each individual acute ischemic stroke patient be considered in the decision of whether or not to perform these studies based on the literature available to date.

Summary: Multimodal Computed Tomography In Acute Stroke Imaging

Recent years have seen the increased utilization of multimodal CT scanning in the emergent diagnostic workup of acute ischemic stroke.[61] Though further advancements in the validation and standardization of advanced imaging methodology are needed as well as research to determine if the use of such modalities results in improved clinical outcomes for patients,[62] the technological advancements of multimodal imaging are indeed reason for excitement in the treatment of acute ischemic stroke. For emergency clinicians, multimodal CT imaging may be employed as a powerful tool to help rapidly identify acute stroke patients who may benefit from emergent IV thrombolytic therapy as well as those who may be better served with referral for immediate endovascular interventions. With the additional benefits of real-time insight into the brain parenchyma at the physiologic level, multimodal CT imaging is likely to replace routine noncontrasted head CT scanning in ED protocols of the future.

Section III: Endovascular Therapies For Acute Ischemic Stroke

Over the past decade, endovascular therapy has revolutionized the management of acute ischemic stroke. Moreover, it has fundamentally altered the way in which emergency clinicians may approach the patient presenting with acute stroke. Traditionally, the only modality available to acute ischemic stroke patients has been IV rt-PA. Unfortunately, < 1% of acute ischemic stroke patients in the United States receive rt-PA, primarily because of a delay in presentation for treatment.[63] As outlined in Section I, the number of patients who receive IV thrombolytic therapy will likely increase with the extended time window of 4.5 hours,[24] but even further expansions of the therapeutic time window are increasingly available with the advancement of endovascular therapies for stroke. Further underscoring the importance of endovascular therapies is the fact that only approximately 20% of patients with large vessel occlusions that receive IV rt-PA actually recanalize.[24,64-66] More specifically, in large vessel stroke, IV rt-PA recanalization rates range from only 10% for internal carotid artery (ICA) occlusion to 30% for middle cerebral artery (MCA) occlusion.[67] The outcome of IV thrombolytic therapy after large intracranial vessel thromboembolic occlusion currently remains dismal and is associated with high morbidity and mortality.[68-71] Because of these data, patients who are not eligible for thrombolytic therapy, who fail to improve after IV rt-PA, or who improve and then worsen (suggesting reocclusion) may be potential candidates for endovascular treatment. There has been a surge in the availability of various endovascular tools to recanalize acute stroke, and recent literature has strongly supported their value. Rha and Saver performed a meta-analysis of 2066 patients across 53 studies and demonstrated that good functional outcomes (mRS score ≤ 2) were more frequent in recanalized patients than nonrecanalized. Additionally, mortality was reduced for recanalized patients.[72]

The Prolyse in Acute Cerebral Thromboembolism (PROACT) trial[73,74] provided evidence that intra-arterial thrombolysis (IAT) was beneficial up to 6 hours following stroke onset. Since these important data were generated, it has been suggested that mechanical thrombectomy recanalizes vessels even faster than IAT, thereby potentially further increasing the benefit of endovascular therapy in late-presenting stroke patients. A number of mechanical thrombectomy trials (Mechanical Embolus Removal in Cerebral Ischemia [MERCI],[75,76] Multi-MERCI,[77] and Penumbra[78]) have demonstrated effective mechanical thrombectomy up to 8 hours following stroke onset. Furthermore, recently published data on consecutive patients treated with IA revascular-ization based upon advanced CT perfusion imaging found no difference in outcomes for patients with known symptom onset of < 8 hours as compared to those with unknown time of onset.[79]

Despite these encouraging data, it must be noted that the value of acute endovascular therapy remains hotly debated. Completion and analysis of a number of ongoing and recently halted trials may dramatically improve our understanding of this debate and may potentially aid in the formation of future clinical investigations. With the anticipation of the continued emergence of endovascular therapeutic options for the treatment of acute ischemic stroke, emergency clinicians may consider these new state-of-the-art approaches to employ in optimizing the care of their patients, whether in their own practice location or through the emergent transfer of appropriate patients to a center with endovascular capabilities.

Intra-Arterial Thrombolysis

IAT may allow higher doses of thrombolytics to be delivered directly to the clot itself, while simultaneously minimizing systemic complications.[80] Because of this, IAT also allows an extended time window and provides a potential treatment option for patients with certain contraindications for systemic thrombolysis. PROACT evaluated IAT with recombinant prourokinase (pro-UK) for patients with < 6 hours of an MCA (M1 or M2 segment) occlusion.[73,74] PROACT-II was a phase III prospective randomized placebo-controlled trial of 180 patients (median NIHSS score = 17, range = 4-30) that demonstrated favorable outcome (mRS score 0-2) in 40% of IA pro-UK patients (9 mg plus low-dose heparin) versus only 25% of controls (low-dose heparin only) ($P = 0.04$).[74] Recanalization was significantly higher for the pro-UK group (66%) than the controls (18%) ($P = < 0.001$). Additionally, while rate of symptomatic ICH was higher in the treatment arm (10%) as compared to controls (2%) ($P = 0.06$), there was no difference in mortality between groups. Unfortunately, IA pro-UK is unavailable in the United States, making rt-PA the IAT agent of choice in the United States. However, despite the widespread utilization of IA rt-PA for the treatment of ischemic stroke in endovascular centers, the FDA has not yet approved its use. The FDA requires 2 Phase III randomized controlled trials, but only 1 has been completed.

The Interventional Management of Stroke (IMS) studies were performed to determine the feasibility and safety of a combined IV and IA approach to thrombolysis. In IMS-I, 80 patients were enrolled within < 3 hours of stroke onset (median NIHSS score = 18).[81] Patients received 0.6 mg/kg of IV rt-PA followed by up to 22 mg of IA rt-PA via a 2-hour infusion until recanalization occurred. IA-treated patients had significantly better outcomes

at 3 months as compared to the NINDS placebo-treated subjects for all outcome measures (OR > 2).[4] Interestingly, outcomes were not significantly improved as compared to the NINDS IV-rt-PA cohort; however, it should be noted that comparable outcomes were demonstrated despite a mean treatment time that was significantly later than that of the NINDS IV-rt-PA cohort (140 minutes versus 90 minutes, respectively).[4]

IMS-II was a nonrandomized safety and feasibility pilot study to evaluate efficacy and safety of combined IV rt-PA (0.6 mg/kg) and IA rt-PA (up to 22 mg). Additionally, a low-energy sonography device could also be used during the infusion in order to potentially increase clot permeability and, as a result, thrombolysis.[82] IMS-II rt-PA-treated patients were significantly more functional at 3 months as compared to NINDS placebo-treated patients for all endpoints (OR > 2.7). Additionally, secondary outcome analysis suggested a benefit versus the NINDS IV rt-PA cohort, although primary outcome analysis did not.[82]

Pooled IMS-I and IMS-II data demonstrated partial or complete recanalization in 75% of ICA terminus and MCA-M1 occlusions, with good reperfusion (Thrombolysis in Myocardial Infarction [TIMI] score 2 or 3) in 61%.[72,83] Good reperfusion (TIMI 2 or 3) was strongly associated with good outcome (P < 0.01). The rate of symptomatic ICH in IMS-II (9.9%) was not significantly different from the NINDS trial rate (6.4%). The attempt for a definitive randomized controlled trial, IMS-III,[84] has recently been halted. IMS-III is a randomized controlled trial of 2 approaches: IV rt-PA versus IV rt-PA combined with an IA approach using thrombolysis and/or a mechanical device. The study was halted for futility, but, importantly, not for safety concerns. The importance of the halting of IMS-III is unclear at this point, but any interpretation of the current literature must incorporate the fact that IAT failed to show efficacy in this trial. According to the IMS-III investigators, the data have yet to be fully analyzed. The stroke community highly anticipates the final results and analysis of this important trial, as this data will likely advance our understanding of the clinical value of IA therapy, or the lack thereof.

Mechanical Thrombectomy

Mechanical thrombectomy for acute ischemic stroke was mostly experimental until the Merci Clot Retriever® (Stryker Neurovascular, Kalamazoo, MI) was approved by the FDA in 2004 (under the 510(k) device approval mechanism) for the removal of intracerebral blood clots. The Merci Clot Retriever® is a flexible nitinol wire with coil loops that is used, in combination with a balloon-guided catheter, to effectively "uncork" a clot from a cerebral blood vessel.[75] The Merci Clot Retriever® was first evaluated in a
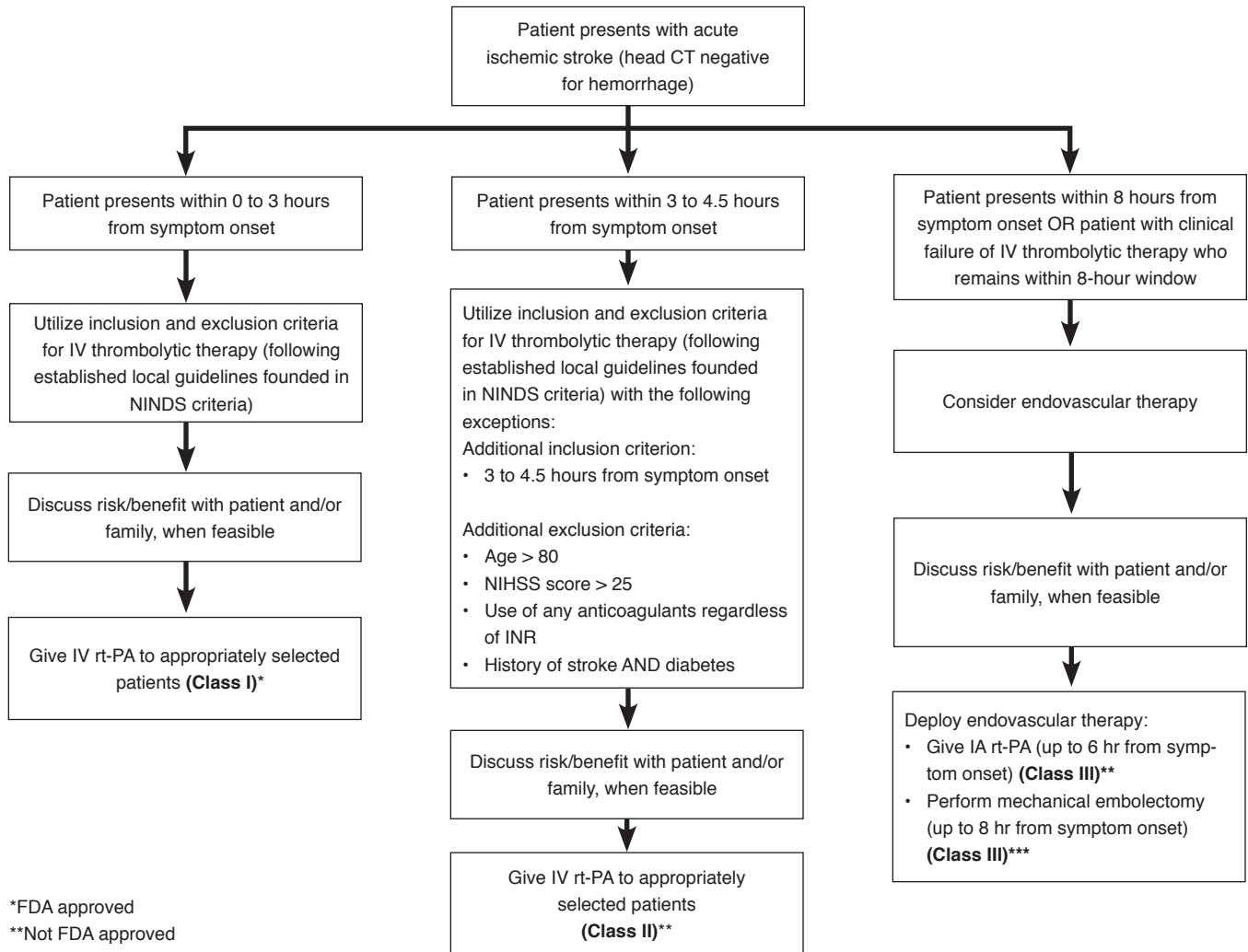
phase I multicenter trial enrolling 30 patients who were ineligible for IV rt-PA or patients for whom IV rt-PA had failed.[76] Successful recanalization was found in 43% of patients using Merci Clot Retriever® alone and in 64% with additional interventions, such as adjuvant thrombolytics. Nine of 18 recanalized patients and zero of 10 nonrecanalized patients achieved significant recovery (mRS score ≤ 3) at 30 days. A 36% mortality at 1 month was also observed; however, no deaths were directly related to treatment with the Merci Clot Retriever® device. Despite these encouraging data, it should be stressed that this is a small study with probable selection bias.

Later, the MERCI trial was undertaken to evaluate the safety and efficacy of the Merci Clot Retriever® within 8 hours of acute stroke onset.[75] This prospective nonrandomized single-arm multicenter trial enrolled 151 patients and achieved a 46% (69 of 151) recanalization rate for patients on intention-to-treat analysis and a 48% (68 of 141) recanalization rate for those in whom the device was deployed.[75] Results were significantly better than expected, as compared to the control arm of the PROACT II study (P < 0.0001).[74] Overall good outcomes (mRS score ≤ 2) were identified in 27.7%, and 3-month good outcomes were 43.5%. Recanalization resulted in more positive neurologic outcomes at 90 days (46% vs 10%) and lower mortality (32% vs 54%) for successfully recanalized patients as compared to those who were not successfully recanalized. Nonetheless, it should be stressed that this was a single-arm study and the cohorts were not randomized.

The Multi-MERCI trial was a prospective multicenter single-arm trial of patients with large vessel stroke treated within 8 hours of symptom onset.[77,85] This investigation was similar to the MERCI trial, but it had the additional objective of evaluating a newer generation (L5 Retriever) device and included patients who experienced failed IV rt-PA therapy. Successful recanalization was achieved in 57% of patients using the Merci Clot Retriever® alone and in 69.5% after adjunctive therapy, such as adjuvant thrombolytics. Overall good clinical outcomes (36%) and mortality (34%) at 3 months were substantially improved versus those in the MERCI trial.[77] Since the introduction of the Merci Clot Retriever® device, approximately 9000 patients have been treated with this mechanical thrombectomy technique.[86] Unfortunately, despite these large numbers, no prospective randomized data, as yet, exist to evaluate the benefit of the Merci Clot Retriever®.

The Penumbra System® (Penumbra, Alameda, CA) is a new generation neuroembolectomy device that was approved by the FDA in 2008, under the 510(k) device approval mechanism, for removal of intracerebral blood clots.[78] This device works by aspiration of the acute clot out of the vessel with direct suction. The suction is further facilitated by a

Clinical Pathway For Management Of Acute Ischemic Stroke In The Emergency Department

```
Patient presents with acute
ischemic stroke (head CT negative
for hemorrhage)
```

Patient presents within 0 to 3 hours from symptom onset	Patient presents within 3 to 4.5 hours from symptom onset	Patient presents within 8 hours from symptom onset OR patient with clinical failure of IV thrombolytic therapy who remains within 8-hour window

Column 1 (0 to 3 hours):

```
Utilize inclusion and exclusion criteria
for IV thrombolytic therapy (following
established local guidelines founded in
NINDS criteria)
```

```
Discuss risk/benefit with patient and/or
family, when feasible
```

```
Give IV rt-PA to appropriately selected
patients (Class I)*
```

Column 2 (3 to 4.5 hours):

```
Utilize inclusion and exclusion criteria
for IV thrombolytic therapy (following
established local guidelines founded
in NINDS criteria) with the following
exceptions:
Additional inclusion criterion:
•  3 to 4.5 hours from symptom onset

Additional exclusion criteria:
•  Age > 80
•  NIHSS score > 25
•  Use of any anticoagulants regardless
   of INR
•  History of stroke AND diabetes
```

```
Discuss risk/benefit with patient and/or
family, when feasible
```

```
Give IV rt-PA to appropriately
selected patients
(Class II)**
```

Column 3 (within 8 hours):

```
Consider endovascular therapy
```

```
Discuss risk/benefit with patient and/or
family, when feasible
```

```
Deploy endovascular therapy:
•  Give IA rt-PA (up to 6 hr from symp-
   tom onset) (Class III)**
•  Perform mechanical embolectomy
   (up to 8 hr from symptom onset)
   (Class III)***
```

*FDA approved
**Not FDA approved
***FDA cleared

Abbreviations: AHA, American Heart Association; CT, computed tomography; ECASS, European Cooperative Acute Stroke Study; ED, emergency department; FDA, United States Food and Drug Administration; IST-3, Third International Stroke Trial; IA, intra-arterial; INR, international normalized ratio; IV, intravenous; NIHSS, National Institutes of Health Stroke Study; rt-PA, NINDS, National Institute of Neurological Disorders and Stroke; rt-PA, recombinant tissue plasminogen activator.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
• Always acceptable, safe
• Definitely useful
• Proven in both efficacy and effectiveness

Level of Evidence:
• One or more large prospective studies are present (with rare exceptions)
• High-quality meta-analyses
• Study results consistently positive and compelling

Class II
• Safe, acceptable
• Probably useful

Level of Evidence:
• Generally higher levels of evidence
• Non-randomized or retrospective studies: historic, cohort, or case control studies
• Less robust randomized controlled trials
• Results consistently positive

Class III
• May be acceptable
• Possibly useful
• Considered optional or alternative treatments

Level of Evidence:
• Generally lower or intermediate levels of evidence
• Case series, animal studies, consensus panels
• Occasionally positive results

Indeterminate
• Continuing area of research
• No recommendations until further research

Level of Evidence:
• Evidence not available
• Higher studies in progress
• Results inconsistent, contradictory
• Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA.* 1992;268(16):2289-2295.

small separator device that morselizes the clot as it is being suctioned. The device was first tested in a European pilot trial, where 23 patients with stroke onset of up to 8 hours were enrolled. Recanalization was achieved in 87% (20 of 23) of patients, although 3 enrolled patients were not treated due to vessel tortuosity.[78] This was followed by a larger prospective multicenter single-arm study (the Penumbra Pivotal Stroke Trial) in which 125 patients were treated within 8 hours of symptom onset.[87] Recanalization was achieved in 81.6% of target vessels, and all-cause mortality was 32.8% at 90 days. Since the Penumbra System® approval, Tarr et al published a retrospective case series of 105 patients from 6 international centers.[88] The mean baseline NIHSS score was 17 for this cohort. Fifty-six percent of patients improved at least 4 points on the NIHSS score by discharge. Following Penumbra System® revascularization, 83.3% of patients had TIMI 2 or 3 recanalization flow. ICH occurred in 6 (5.7%) of patients, and mortality was 21% (22 of 105). These data have led to the Penumbra System® becoming the dominant revascularization tool in the United States. **See Figure 9** for cerebral angiogram images of Penumbra System® intervention.

Angioplasty And Cervico-Cerebral Stenting

For years, angioplasty has been a well-established procedural treatment of arterial thrombosis. Dotter and Judkins published their experience in the use of percutaneous transluminal angioplasty (PTA) for treatment of high-grade atherosclerotic lesions of the peripheral arteries for the first time in 1964.[89] Because of the technical problems in accessing intracranial arteries and the potential complication of inducing stroke due to embolization of debris at the angioplasty site, the study of PTA for cerebral vessels has lagged behind that for other organ systems. In a pilot study for stroke by Nakano et al, successful recanalization was achieved with PTA in 8 of 10 patients with MCA occlusion.[90] The investigators then compared PTA to IAT alone in patients with acute MCA trunk occlusion. Thirty-six patients were treated with IA thrombolytic therapy alone, and 34 patients underwent PTA. Recanalization was significantly higher in the PTA group than the control group, 91.2% versus 63.9%, respectively, and the incidence of symptomatic ICH was reduced in the PTA group (2.9% vs 19.4%). Since then, other studies have also supported these findings with high rates of recanalization, low rates of ICH or systemic bleeding, and significant improvement in neurologic function with combine angioplasty and thrombolysis.[91,92] In addition, many investigations have shown the technical feasibility and high efficacy of PTA in acute ischemic stroke.[93-95]

For improved durability, angioplasty research led to investigation into the use of intravascular stents for the treatment of acute stroke. Stents may be permanently deployed, or, alternatively, can be used in conjunction with thrombolytics for immediate reperfusion followed by retrieval at the end of the procedure. An early case report in 2006 by Levy et al reported the use of stents to treat acute ischemic stroke.[96] The authors successfully used balloon-mounted stents to recanalize a proximal left MCA occlusion. This case report was followed by a larger case series the same year, in which balloon-mounted stents were used in 19 patients.[97] In this case series, stenting was performed only as a rescue procedure after other interventions had failed to recanalize occluded arteries. Recanalization was achieved in 79% of patients. Following the publication of this encouraging data, other case reports and series began to surface in the literature. The Neuroform® (Boston Scientific, Natick, MA), designed for use in the cerebrovascular aneurysm, was used to treat a left MCA occlusion in a 57-year-old woman after unsuccessful attempts at thrombolysis.[98] The stent immediately restored blood flow through the MCA without incident. A year later, Levy et al published the results of a case series utilizing self-expanding stents.[99] Of 19 occlusions in 18 patients, 15 were successfully recanalized, yielding a recanalization rate of 79%. The promising results of these 2 studies led to a prospective trial (SARIS), featuring the Wingspan® SES (Boston Scientific, Natick, MA) as the primary intervention for 20 cases of acute ischemic stroke.[100] All 20 patients achieved recanalization (100%). This study also included the use of the Enterprise® Vascular Reconstruction Device (Codman Neurovascular,

Figure 9. Before And After Images Of Penumbra System® Intervention On Cerebral Angiogram
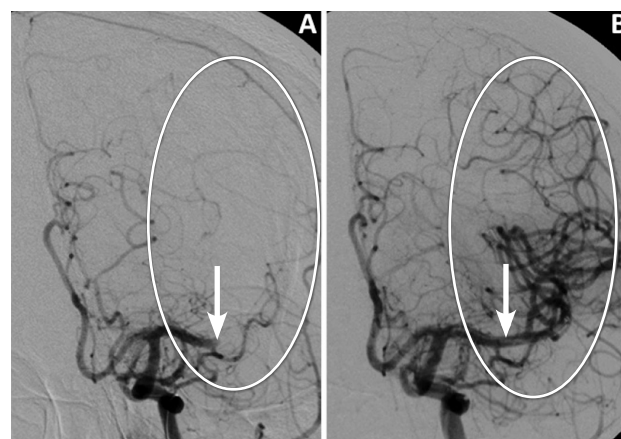
View A shows preintervention image, with arrow demonstrating focal area of arterial occlusion and circle identifying area that is lacking blood supply. View B shows postintervention image, with arrow demonstrating recanalized vessel and circle identifying area that has had blood supply returned after mechanical thromboaspiration.
Image used with permission of J Mocco, MD, MS.

Raynham, MA) for 2 cases in which the Wingspan® could not be navigated through especially tortuous vasculature. The potential relevance of the Enterprise® stent was further supported by a case series of 20 patients, in which the Enterprise® stent achieved an overall recanalization rate (TIMI 2-3 flow) of 100%.[101] Disadvantages such as postprocedure antiplatelet therapy and in-stent stenosis remain serious concerns, and prospective randomized trials are necessary before the role of stents in the treatment of acute ischemic stroke can be defined. Improved patient outcomes also need to be demonstrated in randomized controlled trials.

The interest in stent-based stroke therapy eventually led to the use of stents for temporary endovascular bypass with resheathing/removal of the stent after recanalization is achieved, obviating the need for postprocedure dual antiplatelet therapy. Additionally, this temporizing technique could theoretically eliminate the risk of delayed in-stent stenosis. Kelly et al[102] and Hauck et al[103] reported the use of the closed-cell Enterprise® stent as a temporary endovascular bypass in the acute stroke setting. In both cases, the Enterprise® stent was partially deployed to effect recanalization and then retrieved following successful recanalization.

Based upon these early positive experiences, the concept of using a stent-based thrombectomy device has recently gained major ground. This has most strongly been evident in the recent FDA approval of the Solitaire™ stent (ev3, Irvine, CA). The Solitaire™ was originally designed for assisting coil embolization of aneurysms. The device is a fully recoverable self-expanding stent-based device that can be used as both a temporary endovascular bypass and a thrombectomy device. The device restores flow immediately and avoids the need for the placement of a permanent stent. Additionally, it can be detached like a coil in case a permanent stent is required. The Solitaire™ FR With the Intention For Thrombectomy (SWIFT) trial is a multicenter randomized controlled trial to evaluate the recanalization efficacy of the Solitaire™ FR versus the Merci Clot Retriever® device. The study was halted early secondary to higher mortality in the Merci Clot Retriever® cohort. The trial results were presented at the 2012 International Stroke Conference and announced significantly higher recanalization, lower morbidity, and better clinical outcomes in the Solitaire™ FR cohort. As a result of this study, the Solitaire™ FR is now an FDA-approved technology for use in the United States (under the 510(k) provision). It should be noted, however, that although SWIFT was randomized, it was randomized with Merci Clot Retriever® and not with a placebo control study arm. Therefore, while the positive outcomes observed in the SWIFT trial showed superiority of the Solitaire™ FR to the Merci Clot Retriever®, the

actual clinical benefit of the Solitaire™ FR has not yet been definitively proven.

Other stent-based thrombectomy tools are prevalent in Europe, Canada, and Australia and are soon expected to become available in the United States. The Trevo® device (Concentric Medical Inc., Mountain View, CA) is one of these stent-based thrombectomy devices. The Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO) study was the first evaluation of this technology in a European multicenter prospective clinical trial (Phase III) of randomization to treatment with the Trevo® device or Merci Clot Retriever® device. The trial began in February 2010 and completed enrollment in September 2011. The interim revascularization rate in the first 36 patients was 96%. Thirty patients had 90-day follow-up evaluations, and 63% of these had good outcomes (mRS 0-2).[104] While the trial completed enrollment, the final results are not yet known. However, it is expected that the Trevo® and/or other stent-based thrombectomy devices will soon be approved for use in the United States.

Summary: The Future Of Stroke Revascularization Therapy

The rapid evolution of endovascular stroke therapies over the past decade has dramatically changed the landscape of acute stroke treatment. With multiple new endovascular therapeutic options becoming more widely available, emergency clinicians in most practice setting may employ the option to admit or transfer patients for procedural recanalization strategies in their acute stroke treatment decision protocols. Still, there remains a large amount of heterogeneity in the quality of systems, processes, and technical skill available from center to center. This results in large disparities of care from one institution to the next. It is hoped that clarity will emerge regarding which patients will be most likely to benefit from advances in endovascular stroke treatment. The development of acute stroke treatment appears to parallel the development of acute myocardial infarction treatment 15 years ago, and it is hoped that, sometime in the not-too-distant future, expertise and technological innovation will allow a comparable success to interventional cardiology's dramatic contribution to acute myocardial infarction care. In the meantime, it is important to remember that these devices have not yet been tested against placebo or standard care for improved patient outcomes.

Section IV: Stroke Systems Of Care

The past decade has ushered in a refined understanding of—and commitment to—objective, evidence-based practice of stroke management. Responding to the need for universal, protocol-driven

guidelines for stroke care, the Brain Attack Coalition (BAC) published consensus statements in 2000 and 2005 with recommendations for primary stroke centers (PSC)[105] and comprehensive stroke centers (CSC),[106] respectively. These benchmark publications helped to define a new "standard of care" for stroke patients and established formal certification for stroke centers. While large randomized controlled trials evaluating the efficacy of these guidelines are currently underway, several recent reports suggest that the implementation of BAC recommendations may improve outcomes in patients with acute ischemic stroke. The role of emergency medicine has never been more important, since the majority of these acute stroke patients enter the healthcare system through the doors of EDs. A fundamental knowledge of the developmental history and current status of stroke centers and systems of care will enable the practicing emergency clinician to better understand the importance of these organizational platforms, and in particular, the importance of their critical role in the care of the stroke patient.

Background And Significance

Substantial efforts on the part of those committed to optimizing stroke care have led to the development of hierarchical organizations facilitating the care of stroke patients. Collectively, these initiatives provide a robust framework for improving the care of stroke patients through evidence-based practice, standardized treatment paradigms, and quality-based metrics for continuous reassessment and appraisal. In an initial effort to ensure high-quality standardized care for patients with acute stroke, the BAC was formed. Comprised of members from the American Heart Association as well as professionals from the fields of neurological surgery, neurology, neuroradiology, and emergency medicine, the BAC critically appraised the literature regarding stroke management and instituted recommendations for PSCs and CSCs. PSCs contain the necessary personnel, infrastructure, and programs to treat and stabilize most stroke patients presenting to the ED. CSCs provide care to high-acuity stroke patients who require advanced diagnostic imaging, highly trained specialty physicians, and complex treatment programs. This BAC-recommended "stroke systems of care" model affords the expeditious transport of stroke patients to the appropriate medical facility and improves their overall care. In this section, we discuss the fundamental distinctions between the PSC and the CSC. Given the vital roles of the emergency clinician in the care of acute ischemic stroke, an understanding of the components and capabilities of these centers is vital.

Primary Stroke Centers

The principal goal of the BAC recommendations in 2000 was to improve the outcome of stroke patients by facilitating the appropriate utilization of IV rt-PA and standardizing stroke medical management. The fundamental requirements for a PSC include 24-hour availability of personnel trained in providing acute stroke care, access to neuroimaging, standardized treatment protocols, integration with an EMS and an ED, a dedicated stroke unit, and the necessary infrastructure to report patient outcomes and perform quality improvement analyses.[105] **(See Table 2, page 18.)** These core criteria serve as a scaffold upon which to build and optimize the care of patients with acute stroke. In addition to these original criteria, the BAC published a more-recent summary statement in an effort to further improve patient care at a PSC.[107] In particular, emphasis was placed upon: (1) the importance of acute ED stroke teams, (2) the importance of stroke units with telemetry monitoring, (3) performance of brain imaging with MRI and diffusion-weighted sequences, (4) assessment of cerebral vasculature with MR angiography or CT angiography, (5) diagnostic cardiac imaging, (6) early initiation of rehabilitation services, and (7) formal certification by an independent body, including site visits and quality performance measures. Following the institution of the PSC model, in 2003 The Joint Commission began a formal certification for PSCs in the United States. Ten quality assurance metrics were subsequently established to monitor PSC performance, many of which have since been further refined. Three of these Joint Commission PSC performance measures are particularly relevant to the ED: (1) consideration of thrombolytic therapy in eligible patients, administered within the appropriate treatment window, (2) dysphagia screening, utilizing a bedside swallow evaluation prior to anything by mouth, and (3) early treatment with antithrombotics, initiated by the end of hospital day 2, in patients cleared for swallowing. To date, well over 800 Joint Commission-certified PSCs exist and another 200 to 250 such medical programs have been accredited by state-based agencies and organizations. Therefore, it is likely that nearly every emergency clinician will, at some point in his or her professional career, practice either within a certified PSC or in close geographical proximity to such a center.

Comprehensive Stroke Centers

The majority of stroke patients can be effectively managed at a PSC; however, a minority of patients need a higher-acuity medical setting with specialized personnel providing complex diagnostic and treatment modalities. In 2005, the BAC published a set of guidelines outlining the fundamental components of a CSC.[106] The CSC provides care to individuals with large or complex strokes, hemorrhagic strokes, patients requiring treatment by highly trained subspecialists (eg, endovascular intervention, neurosurgery), or those with multisystem

involvement. These facilities are typically high-volume tertiary care centers with access to complex neuroimaging 24 hours a day, 7 days a week. Moreover, these programs have a specialized infrastructure with programmatic elements (eg, intensive care unit, stroke registry) and have substantial expertise in the diagnosis and treatment of patients with all forms of cerebrovascular disease, with complex endovascular and neurosurgical procedures readily available. **(See Table 3.)** Endovascular procedures would include treatment of aneurysms, arteriovenous malformations, and arteriovenous fistulas; treatment of vasospasm; stenting/angioplasty; IA

Table 2. Major Elements Of A Primary Stroke Center[105,107,108]

Patient Care Elements
- Acute stroke team of at least 2 members (at bedside within 15 minutes)
- Written care protocols (evidence-based and updated)
- Emergency medical services: transport patient to nearest PSC (integrated with stroke center)
- Emergency department: monitoring protocol for patients, vital signs, and neurological status (familiar with protocols and team activation)
- Stroke unit: multichannel telemetry, clinical monitoring protocol (staffed by personnel with training in expertise with stroke)*
- Neurosurgical services (available within 2 hours)
- Neuroimaging services: MRI, MRA, or CTA, and cardiac imaging; may not apply to all patients; not required in acute setting; performed within 6 hours; read within 2 hours of completion (CT or MRI available 24/7)
- Laboratory services: HIV testing; toxicology screening (available 24/7)
- Rehabilitation services: early assessment and initiation (if clinically stable)

Administrative/Support Elements
- Institutional commitment and support
- Dedicated stroke director (reimbursement for call)
- Stroke registry with outcome and quality improvement activities (database and quality improvement program)
- Educational programs: public and professional (ongoing staff and public educational program)
- Administrative support: on-call pay consideration (may improve acute response)
- Center certification: independent organization; performance measures (self-certification not recommended)
- Participation in stroke system of care

*A stroke unit is only required for PSCs that will provide ongoing inhospital care for patients with stroke.

Abbreviations: 24/7, 24-hours a day, 7 days a week; CT, computed tomography; CTA, computed tomographic angiography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; PSC, Primary Stroke Center.

Adapted with permission from Alberts MJ, Latchaw RE, Jagoda A, et al. Revised and updated recommendations for the establishment of Primary Stroke Centers: a summary statement from the Brain Attack Coalition. *Stroke*. 2011;42:2651-2665.

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rt-PA administration; and selective catheter-directed thrombolysis and/or clot retrieval. Neurosurgical procedures available would include obliteration of intracranial aneurysms, arteriovenous malformation, and arteriovenous fistulas; carotid endarterectomy; and decompressive craniectomy).

Since 2005, the BAC has published a list of metrics to be recorded and reported by CSCs to monitor the quality of hospital care and promote improvement.[109] **(See Table 4, page 20.)** These metrics provide a framework for standardizing data collection in an effort to establish national performance standards of stroke care. While there has been no formal certification process for the CSC, several states are trying to implement this policy, and it is anticipated that the Joint Commission will begin the process of certification in the near future.

The Joint Commission has developed a new Disease-Specific Advanced Certification Program for CSCs in collaboration with the American Heart Association and the American Stroke Association. The criteria are available at: http://www.jointcommission.org/certification/advanced_certification_comprehensive_stroke_centers.aspx and are adapted in **Table 4.**

Stroke Systems Of Care

Catalyzed by key initiatives from the BAC, a multitiered, hierarchical program to standardize care for patients with acute stroke has evolved. The tiered levels of a statewide and national stroke system are reminiscent of the historical development and maturation of today's trauma and cardiac systems of care model. The stroke systems of care model places the CSC at the apex of the diagnostic and treatment paradigm, effectively serving patients with complex stroke who are in need of high-acuity care. The PSC serves as a fulcrum, both accepting stroke patients from smaller, community-based hospitals who are in need of more sophisticated management as well as escalating the level of care of complex stroke patients via transfer to a CSC. A third type of stroke system – the Acute Stroke Ready Hospital – has also been proposed in the multitiered approach to stroke care.[108] This program consists of smaller, rural hospitals with a limited number of resources. This hospital, however, displays competence in diagnosing and rapidly triaging stroke patients to a higher level of care (either a PSC or CSC) with thrombolysis capabilities. At a more fundamental level, EMS personnel, most often trained and supervised by emergency physicians, assist in the screening and diagnosis of stroke patients and transport patients to the nearest stroke center based upon local or regional criteria. Continuing the training of EMS personnel, 911 operators, and first-responders in the intricacies of rapid evaluation and management of acute stoke patients will make this process more effective. In ad-

Table 3. Proposed Components Of A Comprehensive Stroke Center[106]

Recommendation	Optional
Personnel With Expertise in the Following Areas	
• Vascular neurology • Vascular neurosurgery • Advanced practical nursing • Vascular surgery • Diagnostic radiology/neuroradiology • Interventional/endovascular physician(s) • Critical care medicine • Physical medicine and rehabilitation • Rehabilitation therapy (physical, occupational, speech therapy) • Staff stroke nurse(s) • Radiology technologist • Swallowing assessment	• Neuroscience intensive care unit • Nursing director for stroke program
Diagnostic Techniques	
• MRI with diffusion • MRA/MRV • CTA • Digital subtraction cerebral catheter angiography • Transcranial Doppler • Carotid duplex ultrasound • Transesophageal echocardiography	• MR perfusion • CT perfusion • Xenon CT • SPECT • PET
Surgical and Interventional Therapies	
• Carotid endarterectomy • Intracerebral aneurysm clipping • Ventriculostomy placement • Craniotomy for hematoma evacuation • Intracranial pressure monitor placement • Endovascular treatment of intracerebral aneurysms and arteriovenous malformation • Intra-arterial reperfusion therapy • Endovascular treatment of vasospasm	• Stenting/angioplasty of extracranial vessels* • Stenting/angioplasty of intracranial vessels*
Infrastructure	
• Stroke unit** • Intensive care unit • Operating room staffed 24/7 • Interventional services coverage 24/7 • Stroke registry	• Stroke clinic • Air ambulance • Neuroscience intensive care unit
Educational/Research Programs	
• Community education • Community prevention • Professional education • Patient education	• Clinical research • Laboratory research • Fellowship program • Presentations at national meetings

*Although these therapies are currently not supported by Grade IA evidence, they may be useful for selected patients in some clinical settings. Therefore, a Comprehensive Stroke Center that does not offer these therapies should have an established referral mechanism and protocol to send appropriate patients to another facility that does offer these therapies.

**Stroke unit may be part of an intensive care unit.

Abbreviations: 24/7, 24 hours a day, 7 days a week; CT, computed tomography; CTA, computed tomographic angiography; MRA, magnetic resonance angiography; MR, magnetic resonance; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

Adapted with permission from Alberts MJ, Latchaw RE, Selman WR, et al. Recommendations for comprehensive stroke centers: a consensus statement from the Brain Attack Coalition. *Stroke.* 2005;36(7):1597-1616.

dition, the advent of telemedicine technologies will help further expedite the transfer of patients to the most appropriate level of care.

Evidence-Based Outcome Measures

Despite overwhelming support for centralization of acute stroke care, a paucity of data to support the belief that this system lowers stroke morbidity and mortality exists. Previous reports have focused on stroke care processes, including the use and timing

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Table 4. Final Certification Eligibility Criteria For Comprehensive Stroke Centers[110]

All standards and requirements for PSC certification are incorporated into the CSC requirements. In addition, eligibility for CSCs includes all of the following requirements:

1. **Volume of cases:**
When applying for initial CSC certification, the organization will need to provide 1 year's data on the volume eligibility criteria. During subsequent recertification for CSC, the volume data for the preceding 2 years, based upon the date of initial certification, will be required.

The CSC will demonstrate:
- That care has been provided to 20 or more patients/year with the diagnosis of subarachnoid hemorrhage
- That 10 or more craniotomies for aneurysm clipping procedures are performed per year
- That 15 or more endovascular coiling procedures for an aneurysm are performed per year
- That the CSC will administer IV rt-PA to 25 eligible patients per year
  - Note 1: Providing IV rt-PA to an average of 25 eligible patients over a 2-year period is acceptable
  - Note 2: IV rt-PA administered in the following situations can be counted in the requirement of 25 administrations per year:
    - IV rt-PA ordered and monitored by the CSC via telemedicine at another hospital
    - IV rt-PA administered by another hospital which then transferred the patient to the CSC
2. **Advanced imaging capabilities:**
The hospital will be able to provide:
- Carotid duplex ultrasound
- Catheter angiography onsite 24 hours a day, 7 days a week
- CTA available onsite 24 hours a day, 7 days a week
- MRA available 24 hours a day, 7 days a week
- Transcranial Doppler
- Transesophageal echocardiography
- Transthoracic echocardiography
3. **Posthospital care coordination for patients**
4. **Dedicated neurointensive care unit beds for complex stroke patients**
5. **Peer review process to review and monitor the care provided to patients with ischemic stroke, subarachnoid hemorrhage, and administration of rt-PA**
6. **Participation in stroke research**
7. **Performance measures**

Abbreviations: CSC, Comprehensive Stroke Center; CTA, computed tomographic angiography; IV, intravenous; MRA, magnetic resonance angiography; rt-PA, recombinant tissue plasminogen activator.

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of thrombolytic therapy.[111-113] Overall, these efforts have been successful in promoting the increased use of rt-PA in the United States[111]; however, critical analysis of PSC performance measures demonstrates that adherence to BAC-implemented diagnostic and treatment regimens correlates with improved stroke care.[114-116] One study of acute ischemic stroke conducted in Finland demonstrated that admission to a CSC resulted in a 2.4% reduction in mortality as compared to a non-CSC hospital.[117] Similarly, admission to a PSC also correlates with a 1.5% decrease in stroke mortality as compared to a non-PSC institution.[117] More recently, Xian et al published a large observational study comparing the mortality of patients with acute ischemic stroke admitted to designated stroke centers versus nondesignated hospitals.[118] They found that admission to a designated center was associated with a 2.5% absolute reduction in 30-day all-cause mortality ($P < 0.001$) and increased use of thrombolysis therapy ($P < 0.001$). This survival benefit persisted for up to 1 year after stroke occurrence and was independent of patient and hospital variables. Intriguingly, the lower mortality was specific to stroke and was not found in other life-threatening conditions, suggesting that the mortality benefit was specific to stroke center designation. While it would be difficult to delineate the specific BAC criteria responsible for improving stroke mortality in this setting, it is likely that the combination of these guidelines lays a critical foundation for optimizing the medical and surgical management of acute stroke patients.

Notably, despite increasing evidence that adherence to evidence-based guidelines improves the outcome of patients with stroke and transient ischemic attack, many patients fail to receive recommended interventions.[30] For this reason, Get With the Guidelines®-Stroke (GWTG-Stroke)—a national quality improvement program—was created by the American Heart Association and the American Stroke Association to determine whether adherence to objective stroke management guidelines improves overall patient care. This initiative was a voluntary, unfunded effort on the part of hospitals committed to excellence in the management of stroke patients. In this multicenter prospective nonrandomized trial, GWTG-Stroke demonstrated that program participation resulted in improvements in 7 predesignated performance measures (eg, IV thrombolytics, early antithrombotics, deep venous thrombosis prophylaxis, discharge antithrombotics, anticoagulation for atrial fibrillation, aggressive treatment for hyperlipidemia, and smoking cessation) and 1 composite measure. In addition, this study showed that increased adherence to stroke performance measures resulted in marked improvements in stroke care.[5] Importantly, this initiative could translate into significant cost savings over the long term. Today, over

85% of the United States population lives within 1 hour of a GWTG-Stroke hospital.

Whether the BAC-recommended, Joint Commission-certified program model for stroke management truly improves stroke care remains to be validated. One potential criticism of this model is that hospitals adopting BAC recommendations were already committed to quality improvement and that the process of Joint Commission certification may simply reflect an otherwise self-motivated drive for excellence. The fact that a recent study of Joint Commission-certified stroke centers found that certified hospitals documented superior stroke outcomes even before certification began supports this contention.[119] Nevertheless, it is difficult to ignore that, from 1997 to 2007, the annual stroke death rate decreased 34.3%, according to the 2011 Heart Disease and Stroke and Stroke Statistics Update.[120]

Summary: Stroke Systems Of Care

Since the original publication of PSC guidelines by the BAC in 2000, previously fragmented stroke care organizations have begun to coalesce into a standardized, multifaceted system for care of patients with acute stroke, with emergency medicine leading the way. While prospective randomized trials validating the benefits of the PSC/CSC model are currently lacking, an increasing body of evidence supports the outcomes achieved by implementing stroke systems of care. Together, these initiatives have culminated in an increased utilization of IV rt-PA, and—along with evidence-based early primary and secondary prevention—have improved care for stroke patients. Although significant advances in centralized stroke management have been made, the field remains a work in progress. With the advent of new diagnostic and therapeutic options and the evolution of evidence-based guidelines, the stroke systems of care model will continue to be further improved and refined. Emergency medicine will continue to be at the forefront in the evolution and improvement of stroke care for all patients.

Conclusion

The present time is an exciting one in the stroke community, as the cutting edge of acute stroke care continues to evolve. With advancements in the emergent management of stroke, emergency clinicians may be encouraged by increasingly more opportunities to positively affect the care of patients with acute ischemic stroke. As the study and refinement of these new treatment strategies continues, hope grows stronger that more and more patients will be eligible for and more effectively selected for state-of-the-art reperfusion therapies. As a result, the potential to decrease the terrible morbidity and mortality associated with acute stroke serves as a driving force in the quest to improve the emergent care of stroke patients. At the forefront of emergent stroke care, emergency clinicians have an opportunity to make a tremendous impact in the care of these patients, whether by the continuous improvement of their own stroke center practice or with the development of expeditious transfer protocols to afford their patients the most advanced therapies available today.

Case Conclusions

You recognized the severity of the patient's acute ischemic stroke and responded quickly. With the knowledge of ECASS III data on extending the rt-PA window to 4.5 hours, you immediately consulted with your stroke neurologist. You treated the patient with IV rt-PA and admitted him to your stroke unit, where he had a meaningful neurological recovery.

Realizing that the patient is suffering from a wake-up stroke and has an unknown time of symptom onset, you considered your options. You decided to obtain multimodal CT imaging, which demonstrated an MCA occlusion along with a very large penumbra but only minimal core infarct. After consultation with your local stroke team, you sent the patient for endovascular therapy. There, rapid recanalization of his MCA was achieved. The patient had a dramatic improvement in his condition, and he walked out of the hospital 2 days later. (See the example case in Section II, an actual case.)

With the understanding that your patient was beyond the extended window for IV thrombolytic therapy, you explored your options. You knew that a local hospital performed endovascular therapies, so you called the interventionalist on call. The interventionalist accepted the patient in transfer, and you quickly sent your patient to the outside hospital. There, they deployed a mechanical endovascular device and achieved prompt reperfusion of the patient's occluded right MCA. Within days, she was back to working in her garden and enjoying her grandchildren.

Risk Management Pitfalls For Acute Ischemic Stroke

1. **"I realized that the patient met criteria for thrombolytics, but I was afraid she would have a hemorrhage if I gave thrombolytics, and I would get sued."**
   There are far more lawsuits filed against emergency physicians for failure to administer thrombolytic therapy than for complications of the treatment. Adherence to a well-developed acute stroke protocol agreed upon by local practice is the best defense in any malpractice scenario.

2. **"I didn't realize the patient was anticoagulated before I gave thrombolytic therapy."**
   A thorough review of the patient's medication and allergy list is always indicated prior to the administration of any drug. If a patient is on warfarin, the patient's INR must be known before thrombolytics are administered. If the patient is on warfarin and is beyond the 3-hour treatment window, IV thrombolytics are contraindicated, per ECASS III guidelines.

3. **"I gave the patient thrombolytics for the stroke, but the patient had a massive gastrointestinal hemorrhage. I didn't realize he had a significant gastrointestinal bleed a week ago."**
   A thorough review of the indications and contraindications of thrombolytic therapy is always indicated prior to the initiation of treatment. Careful attention to the contraindications for therapy will help the practitioner avoid pitfalls.

4. **"I didn't see the hemorrhage on the CT scan."**
   Rapid interpretation of the noncontrasted head CT for hemorrhage is essential to successful thrombolytic therapy. The expertise to identify acute hemorrhage is paramount when interpreting this study prior to the administration of thrombolytic therapy. If one is uncomfortable making this determination, rapid access to adequate radiologic expertise must be a part of any acute stroke treatment protocol.

5. **"We didn't realize the patient was having a stroke until it was too late. The symptoms were mild, and the patient was in our waiting room for 3 hours before he was brought back."**
   In the era of significant ED overcrowding, accurate and timely triage is paramount. Easy-to-follow information on the signs and symptoms of stroke should be made available to all triage personnel, with an understanding to immediately bring any patient meeting suspicion for acute stroke to the attention of the attending ED physician.

6. **"I really thought it was conversion disorder."**
   A robust knowledge of the signs and symptoms of stroke as well as insight into more unusual presentations for stroke, coupled with a thorough and expert neurological examination, are critical in avoiding the misdiagnosis of an acute stroke as a manifestation of psychiatric illness. Beware of cognitive biases, and make sure that all patients with any alterations in baseline function receive very careful consideration.

7. **"It seemed like benign positional vertigo to me."**
   Vertigo can be very difficult to differentiate in its etiology. When in doubt, consider posterior circulation ischemia as an etiology, especially when additional symptoms (double vision, coordination problems, difficulty walking, etc.) are present.

8. **"The patient came into the ED 5 hours into his acute stroke. It was too late to do anything."**
   Be aware of surrounding resources in acute stroke care. If you do not practice in a center that offers endovascular therapies that can be deployed long after IV thrombolytic windows close, know whether or not surrounding facilities offer such therapies. Some lawsuits arise because of a failure to consider transferring a patient to a higher level of care when the patient remains within endovascular therapeutic windows but does not receive an opportunity for treatment.

9. **"Everything was going fine, but it took too long to get the CT done."**
   Time targets for the completion of emergent studies are well-established. Delays in the acquisition of emergent studies are commonly cited as deviations in the standard of care by plaintiffs. Well-designed acute stroke protocols — in place and rehearsed prior to patient arrival — serve to streamline the care of stroke patients, optimizing care and minimizing delays.

10. **"I can't believe she had a stroke. The neck pain seemed musculoskeletal."**
    Remember that cerebrocervical arterial dissections may occur following blunt trauma to the neck as well as spontaneously. Know the risk factors for carotid and vertebral artery dissections and consider the diagnosis in any case of headache, neck pain, or vertigo or with any neurologic symptoms, especially following trauma to the head or neck or in any other risk-associated scenario.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.

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CME Questions

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1. **The FDA-approved window for IV rt-PA treatment in acute ischemic stroke is:**
   a. 1.5 hours
   b. 3.0 hours
   c. 4.5 hours
   d. 6.0 hours

2. **Which of the following was used as an exclusion criterion for ECASS III and thus serves as a contraindication to IV thrombolytic therapy within the 3- to 4.5-hour treatment window?**
   a. A combination of a history of prior stroke and hypertension
   b. Age > 85 years
   c. Any use of anticoagulant therapy
   d. NIHSS score > 30

3. **A hyperdense artery sign on noncontrasted CT scan of the head in an acute ischemic stroke patient indicates:**
    a. An acute hemorrhage
    b. An acute infarction
    c. Severe arteriosclerotic disease
    d. An acute thrombus

4. **The primary use of data gathered from multi-modal CT scanning in the emergent management of stroke is to:**
    a. Establish a measurement of cerebral blood flow
    b. Establish a measurement of cerebral blood volume
    c. Establish a measurement of mean transit time
    d. Differentiate between ischemic core and penumbral tissue

5. **A potential clinical application of multimodal CT scanning is to:**
    a. Identify patients suffering a wake-up stroke who might still benefit from reperfusion
    b. Identify patients who might benefit from therapy despite an INR > 3
    c. Identify patients who might benefit from hypothermia treatments
    d. Identify patients who are suffering from an acute hemorrhage

6. **A potential advantage to the use of endovascular therapies for acute ischemic stroke is that:**
    a. Endovascular therapies can usually be deployed faster than IV treatment.
    b. Large vessel occlusions are unlikely to resolve with IV treatment alone.
    c. Endovascular therapies have a lower intracranial hemorrhage rate than IV therapy.
    d. Endovascular therapies are less expensive than IV therapy.

7. **The highest endovascular recanalization rates reported in the literature have been seen with the use of:**
    a. Intra-arterial rt-PA
    b. Intra-arterial urokinase
    c. The Merci Clot Retriever®
    d. The Penumbra System®

8. **Which of the following is a required component of a Primary Stroke Center?**
    a. IV rt-PA treatment in at least 75% of patients
    b. The use of multimodal CT scanning 24/7
    c. ED familiarity with protocols and stroke team activation
    d. The presence of an in-house neurologist 24/7

Abbreviations

ATLANTIS: Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke
BAC: Brain Attack Coalition
CSC: Comprehensive Stroke Center
CT: Computed tomography
CTA: Computed tomographic angiography
DRAGON: Dense cerebral artery sign/early infarct sign, Rankin Scale score, Age, Glucose level at baseline, Onset-to-treatment sign, baseline NIHSS score
ECASS: European Cooperative Acute Stroke Study
IA: Intra-arterial
IAT: Intra-arterial thrombolysis
ICH: Intracerebral hemorrhage
IMS: Interventional Management of Stroke
IST-3: Third International Stroke Trial
IV: Intravenous
MCA: Middle cerebral artery
MERCI: Mechanical Embolus Removal in Cerebral Ischemia
MRA: Magnetic resonance angiography
mRS: modified Rankin Scale
MTT: Mean transit time
NIHSS: National Institutes of Health Stroke Scale
NINDS: National Institute of Neurological Disorders and Stroke
PSC: Primary Stroke Center
rt-PA: Recombinant tissue plasminogen activator
sICH: Symptomatic intracerebral hemorrhage
SITS-ISTR: Safe Implementation of Thrombolysis in Stroke – International Stroke Thrombolysis Registry
SITS-MOST: Safe Implementation of Thrombolysis in Stroke – Monitoring Study

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