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A New Era of Extended Time Window Acute Stroke Interventions Guided by Imaging

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Abstract

Ischemic stroke is one of the most debilitating and deadliest conditions worldwide. Intravenous t-PA is the current standard treatment within 4 hours after onset of symptoms. Recent randomized controlled trials have demonstrated the efficacy of neurointerventional intra-arterial treatment in acute ischemic stroke. About 20% of acute ischemic stroke are classified as wake-up strokes, which falls out of the conventional treatment time window. New evidence suggests that some patients with longer time from symptom onset (up to 24 hours) may benefit from thrombectomy, probably in part due to variations in collateral circulation among individual patients. Advanced imaging can play a crucial role in identifying patients who could benefit from endovascular intervention presenting within extended treatment time windows. In this article, we review the advanced imaging algorithm for ischemic stroke workup in the multiple studies published to date and summarize the results of the clinical trials for late ischemic stroke that can be clinically useful.

Keywords

late onset stroke, stroke treatment, stroke imaging, acute stroke therapy, MRI, CT

Introduction

Intravenous t-PA (IV-tPA) is effective in treating patients with acute ischemic stroke up to 4 hours after symptom onset, and endovascular thrombectomy was previously indicated for patients up to 6 hours after symptom onset.[1-3] Wake-up strokes, which represent 1 in 5 acute ischemic strokes,[4] and strokes having an unknown time-of-onset frequently fall outside these treatment time windows.

All evidence supports the concept that minimizing time to treatment is critical. New evidence suggests that in some patients with prolonged time from symptom onset to treatment (up to 24 hours) may still benefit from intervention due to variations in collateral circulation.[5-15] Advanced computerized tomography (CT) or magnetic resonance imaging (MR/MRI) perfusion imaging (CTP/MRP) may identify patients who would benefit from thrombectomy.[9] For example, imaging can identify patients with large diffusion/perfusion mismatches in whom treatment beyond the conventional 6 hours treatment window would benefit.[13] Such data support the rationale that cerebrovascular physiology may be a better prognosticator of outcome rather than time alone. Herein, we review the advanced imaging algorithm for ischemic stroke workup, summarize results of clinical trials for late ischemic stroke and describe features of these trials.

Which Stroke Patients Should be Considered for Neurointerventional Therapy?

When cerebral blood flow (CBF) drops below a critical threshold, there is a disruption of energy metabolism, resulting initially in neurologic symptoms. Further reduction will produce cytotoxic edema and cell death within minutes, which can be identified by a reduction in the apparent diffusion coefficient on Diffusion-Weighted Imaging (DWI).[16-18] Prompt reperfusion can limit and even reverse this cascade.

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While multiple parameters need to be considered when deciding when patient should receive reperfusion treatment, the most important include the time window between symptom onset and presentation and imaging-based assessment of perfusion collateral flow.

Time Window

Stroke patients who present beyond 4 hours after symptom onset are not candidates for IV thrombolysis per current guidelines.[1,3] Endovascular thrombectomy trials, however, have demonstrated benefit for stroke patients up to 6 hours after symptom onset.[19-24] Newer trials such as DWI or CTP assessment with clinical mismatch in the triage of wake-up and late presenting strokes undergoing neurointervention with Trevo (DAWN) and endovascular therapy following imaging evaluation for ischemic stroke 3 (DEFUSE 3), extended this time window even further, showing benefit of endovascular thrombectomy for patients up to 24 hours following symptoms onset.[5,6] a study of intravenous thrombolysis with Alteplase in MRI-selected patients (MR WITNESS) and efficacy and safety of MRI-based thrombolysis in wake-up stroke (WAKE UP) stroke trials showed that administration of intravenous thrombolysis was successful within 24 hours of stroke onset in some patients.[7,8] The salvageability of brain tissue largely depends on the degree of collateral perfusion of the ischemic territory. Individual patient variability in diffusion/perfusion mismatch volume on advanced imaging will direct subsequent treatment.[25] Given this new data, the clinician and radiologist should be prepared to screen and administer thrombolytic or endovascular therapy within 24 hours of stroke onset.

Time is a surrogate for stroke viability. The majority of individuals infarct in a predictable time pattern such that the risk of revascularization outweighs the benefit after 6 hours poststroke. However, perfusion imaging techniques can individualize treatment irrespective of time based on an individual's own collateral flow characteristics. Many individuals within the extended time window will not have a favorable mismatch but perfusion imaging allows us to find those individuals who do.

Imaging Inclusion Criteria

Based on recent evidence, a patient presenting within 6 hours of stroke symptom onset typically should be evaluated with noncontrast CT and CT angiogram (CTA), which could be sufficient for patient selection for thrombectomy as shown in multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands (MR-CLEAN).[19] If the patient has a proximal vessel occlusion on CTA, no intracranial hemorrhage and an Alberta stroke program early CT score (ASPECT) score of >6, he or she may benefit from intra-arterial (IA) therapy. If available, CTP and MRI can be useful. For the high-risk group presenting from 6 hours to 24 hours after onset, however, accurate determination of core and viable tissue is critical. Magnetic resonance imaging is the most sensitive and specific imaging modality for determination of infarct core and viable penumbral tissue. However, in the absence of emergent MRI, CTP can address this as well. A core volume on DWI of less than 70 mL has been found to be a reliable MR inclusion criteria for thrombectomy in late presenting patients.[6] For CTP, a mismatch of cerebral blood volume or CBF (core) and mean transit time or time to maximum (Tmax > 6 seconds; viable hypoperfused tissue) suggest the presence of tissue at risk in patients presenting with proximal vessel occlusion in the anterior circulation. A core volume less than 70 mL and a ratio of ischemic tissue to initial infarct volume of 1.8 or more can be used to identify those who may benefit from reperfusion.[6] A simple decision algorithm addressing when to perform endovascular therapy by imaging criteria and time of stroke onset has recently been developed (Figure 1).[26]

Diffusion MRI. Diffusion MRI is the most specific method for the early detection of the acute ischemic stroke.[27-29] Diffusion MRI is the most reliable estimate of the ischemic core, which represents the irreversibly injured tissue or the "core" of the infarct.[30-33] A meta-analysis found that the ischemic core is independently associated with functional independence and outcome.[34] Previous studies have also shown that a DWI abnormality volume of >70 mL is associated with a poorer outcomes regardless of reperfusion status.[18,35,36] Infarct core volumes below this threshold are associated with significantly better outcomes with treatment and can be used to select patients for endovascular intervention.[37]

A core on DWI <70 mL in patients with a proximal vessel occlusion on CTA suggests that a sizable area of viable tissue is present. Small volume core infarcts were seen in infarcts at >8 hours from symptom onset, suggesting that in some patients, a sizable volume of viable tissue can potentially be salvaged among even patients with delayed presentations.[38]

To identify those patients who would benefit from acute reperfusion therapy, many imaging parameters have been studied. CT angiogram or magnetic resonance angiography (MRA)-DWI mismatch suggests the presence of viable tissue when there is proximal vessel occlusion.[38-40]

Computed tomography and MR perfusion. The volume of salvageable brain tissue in late presenting acute ischemic stroke patients is determined in part by the degree of collateral circulation. Patients with rich collaterals are more likely to have salvageable brain tissue in the delayed time window (>6 hours) compared to patients with poor collaterals.[41] However with perfusion imaging, we are able to find these individuals to administer the treatment they need. Multiple trials used perfusion parameters such as CBF, cerebral blood volume, mean transit time, and Tmax values for patient selection in determining who received neurointerventional treatment.

In the DEFUSE-3 trial, patients were selected for endovascular treatment if the ratio between the volumes of

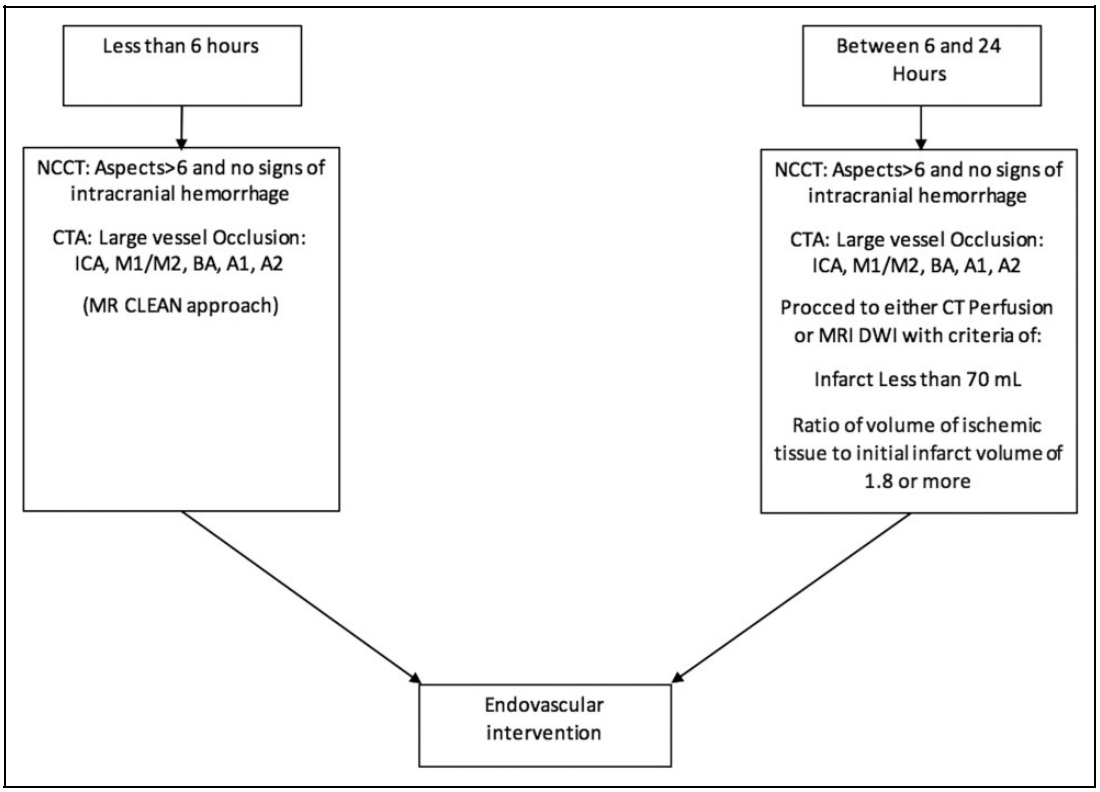

Figure 1. Endovascular therapy decision algorithm for acute large vessel ischemic stroke.

hypoperfused tissue and the ischemic core (mismatch ratio) was $\geq$1.8, with an absolute difference (mismatch volume) of $\geq$ 15 mL, and if the ischemic core volume (CBF) was <70 mL on CTP or MRP.[6] Tmax >6 seconds was used as an indicator for hypoperfused tissue and CBF <70 mL was used as an indicator for core on CTP or MRP.

The EXTEND trial used similar inclusion criteria to DEFUSE 3. Patients were selected if the perfusion lesion-ischemic core mismatch was greater than 1.2, an absolute difference of $\geq$10 mL, ischemic core volume of <70 mL.[20]

A mismatch between MRP and diffusion is also used to determine the volume of salvageable tissue. The DAWN and DEFUSE 3 trials showed that patients with MRP-DWI mismatch benefit from endovascular therapy well beyond the 6-hour window.[5,6,42] The DAWN trial focused only on intracranial carotid occlusions (ICAs) while DEFUSE-3 included both carotid and cervical ICAs with or without tandem middle cerebral artery lesions, detected either on CTA or MRA.[5,6] Both DAWN, DEFUSE-3, and EXTEND trial defined the size of penumbra using a volume of injected tracer agent that was delayed greater than 6 seconds (Tmax > 6 seconds).

Available Treatment Options

There are 2 treatment options available for ischemic stroke: thrombolytic and endovascular therapy. Most of the late-presenting acute ischemic stroke trials compare endovascular therapy to standard medical care. Recently, several randomized controlled trials, such as MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, REVASCAT, and THRACE have demonstrated benefit in treating stroke patients within 6 hours of symptom onset.[19-24] The goal of late presenting acute ischemic stroke trials was to determine whether thrombolytic or endovascular therapy also benefit patients who fall outside the 6-hour window for up to 24 hours.

Outcome Measures

The primary outcome measure is functional outcome as measured by the modified Rankin Scale (mRS) at 90 days. Secondary outcomes are a combination of imaging findings, such as parenchymal hematoma, recanalization rate, lesion growth, and final infarct volume, as well as clinical findings of symptomatic intracranial hemorrhage (sICH) and mortality.

Modified Rankin scale. In the DAWN and DEFUSE-3 trial, thrombectomy with medical therapy greater than 6 hours after stroke onset with mismatch of severity of the clinical deficit and the infarct volume significantly decreased poststroke disability and improved functional independence (mRS 0-2) at 90 days post stroke when compared to medical management alone.[5,6] This suggests that a dual approach with IV-tPA and endovascular treatment may produce synergistic benefits for revascularization.

Table 1. Ongoing Studies of Interventions for Anterior Circulation Acute Ischemic Stroke in Extended-Time Windows.

Trial Name	Inclusion Criteria	Treatment	Comparison	Imaging Criteria	Imaging Exclusion Criteria	Trial Identifier
POSITIVE	Late <12 hours/ unknown time onset	Endovascular	Standard of care	Penumbra: MRI/CTP, proximal occlusion	ASPECT<7, Infarct>1/3 MCA	NCT 01852201
THAWS	4.5-9 hours of symptom onset, or after wake-up stroke	Tissue Plasminogen Activator	Standard of care	MR-DWI or CT-CBF: infarct core lesion of less than or equal to 70 mL	Infarct core >1/3 MCA territory, coextensive early ischemic change in brainstem or cerebellum	NCT 02002325
WASSABI	Late/unknown onset, within 24 hours of symptom onset	Endovascular, IV thrombolysis	Standard of care	CTP shows evidence of penumbra	CT shows intracranial hemorrhage	NCT 01455935

Abbreviations: ASPECTS, Alberta Stroke Program Early CT score; CBF, cerebral blood flow; CTP, CT perfusion; IV, intravenous.

Variability in endovascular treatment techniques may account for differences in outcome in late acute ischemic stroke studies. Two out of the 6 studies utilized stent retrievers.[43,44] DAWN and DEFUSE 3 have shown that stent retrievers are feasible after 6 hours.[5,6]

Recanalization rate. High recanalization rates of 89% to 100% have been reported using stent-retrievers in patients with known short-time window presentations,[44,45] while slightly lower recanalization rates of 77% to 79% are reported in those presenting later.[5,6] Benefit of endovascular treatment has been strongly associated with degree of recanalization with use of Thrombolysis in Cerebral Infarction scale.[46] With regard to IV-tPA, the EXTEND trial reported a recanalization rate of 67.3% within 24 hours of treatment. Although definitive results for late presentation patients is pending, there is emerging evidence that successful recanalization rate is associated with smaller final infarct volume, smaller infarct growth, and improved functional outcome at 90 days in both wake-up and nonwake-up stroke patient groups.[47]

Complications

Mortality rate. Mortality rates at 90 days are similar for the 3 studies with these secondary metrics. DAWN reported 19% mortality at 90 days in the endovascular treatment group, compared to 18% in the medical-therapy group,[5] while DEFUSE-3 reported 14% mortality at 90 days in the endovascular-therapy group and 26% in medical therapy.[6] EXTEND stated a mortality rate of 11.5% in the IV-tPA group compared to 8.9% in the placebo group.

Intracranial hemorrhage. Hemorrhagic transformation is a major complication in patients who undergo endovascular therapy.[48,49] Changes in blood–brain barrier permeability and loss of CBF autoregulation are thought to allow for post-therapy hyperperfusion.[50] A majority of ongoing randomized control trials to assess endovascular therapy in late acute stroke patients (Table 1) exclude patients with large ischemic lesions greater than a third of the MCA territory or acute or chronic ICH which may be a proxy for posttreatment ICH risk. Symptomatic intracranial hemorrhage occurred in 2% to 28% of patients included in these late acute ischemic stroke trials (Table 2). However, DAWN and DEFUSE 3 showed no difference in sICH rate in endovascular treatment versus medical therapy.[5,6]

Current Issues

Use of NIHSS Score for Intervention Criteria

In prior years—before modern stent-retrievers and aspiration catheters made embolectomy more efficacious and less risky than prior techniques—a low NIHSS was considered an important exclusion criterion for IA tPA administration. Currently, the NIHSS is used to quickly identify patients with large vessel occlusions who are potential treatment candidates. There is a debate about how to treat patients with low NIHSS and M1 occlusions. Sarraj et al performed a retrospective analysis of stroke patients who had a NIHSS score <6 and received endovascular treatment. They showed that treatment was ineffective compared to those who were medically managed.[51]

Initial neurological status is the single most important predictor of stroke outcome.[52] A higher NIHSS increases the pretest probability of identifying lesions on imaging and is a predictor for length of stay, outcomes, and discharge disposition.[52] Trials like DAWN and DEFUSE 3 have shown good outcomes in patients with moderate NIHSS scores. One rationale for selecting patients with severe neurological deficits is the higher likelihood of success for using endovascular therapy to remove a large clot. Some neurointerventionalists choose to treat dominant M2 MCA occlusions with a relatively low NIHSS if the symptoms include aphasia, as it is a particularly devastating neurological deficit.

Table 2. Studies of Interventions During the Extended Time-Windows for Acute Ischemic Stroke.

Authors	Study Design	Time Window	Imaging Inclusion Criteria	Patients (n)	Treatment Type	Mean NIHSS	sICH	mRS 0-2 at day 90	Outcome Measures	Results
Lansberg et al (Defuse 2)	Prospective multicenter trial	<12 hours	MRI: DWI/PWI mismatch	138	Endovascular (some patients had initial IV tPA)	14 (median)	7%	55%	Functional outcome, lesion growth, symptomatic ICH, parenchymal hematoma	Favorable clinical outcomes with IA therapy in mismatch group
Nogueira et al (DAWN)	Multicenter RCT	6-24 hours	Mismatch: small DWI/CTP	206	Endovascular	17	6%	49%	Disability, Functional outcome, safety	Favorable outcomes with endovascular treatment
Albers et al (DEFUSE 3)	Multicenter RCT	6-16 hours	Multimodal CTA, MRA, CTP, MRP, MR DWI	182	Endovascular	16	7%	45%	Functional Outcome, Mortality, Safety	Favorable outcomes with Endovascular Treatment
Schwamm et al (MR Witness)	Prospective multicenter trial	< 24 hours and <4.5 hours of treatment initiation	MR confirms acute ischemic stroke and diffusion-flair mismatch	80	IV-tPA	7	27.5%	39% (mRs 0-1)	Functional outcome, mortality, safety	Favorable outcomes with IV-tPA therapy with DWI-FLAIR mismatch
Thomalla et al (WAKE-UP)	Multicenter RCT	>4.5 hours of treatment initiation	MR DWI, FLAIR, MRA, DWI-FLAIR mismatch	503	IV-tPA	6 (median)	2.0%	53.3% (mRs 0-1)	Disability, functional outcome, mortality, parenchymal hematoma	Favorable outcomes with IV-tPA therapy with DWI-FLAIR mismatch
Ma et al (EXTEND)	Multicenter RCT	< 24 hours of symptom onset 4.5-9 hours of symptom onset, or after wake-up stroke	MR DWI, CT/MR Perfusion	225	IV-tPA	12 (median)	6.2%	49.6%	Disability, functional outcome, mortality, parenchymal hematoma	Favorable outcomes with IV-tPA therapy

Abbreviations: CTA, CT angiogram; CTP, CT perfusion; DWI, diffusion-weighted imaging; IA, intra-arterial; IV-tPA, intravenous t-PA; mRS, modified Rankin scale; MRI, magnetic resonance imaging; PWI, perfusion-weighted imaging; sICH, symptomatic intracranial hemorrhage.

Routing Patient to a Stroke Center

Given that a stroke is a time sensitive disease, it is important for the patients to be directed to the appropriate facility to get the care they need. A 2017 study Rinadlo et al showed that patients with acute ischemic stroke who were transferred to a high volume stroke center to receive endovascular therapy had reduced mortality rate.[53] With the new evidence developed from DAWN, DEFUSE 3, WAKE-UP, and MR WITNESS trials, patients who live hours away from a primary stroke center should still be transported. It is possible to break down routing into a 2-step system based on imaging, where the first set of imaging can be done at a nonstroke center to determine whether transport is necessary. Second set of imaging can be done at a primary stroke center where core imaging with DWI or CTP can be performed.

Types of Anesthesia Used in Endovascular Treatment

There has been a debate over which anesthesia technique (general anesthesia [GA] vs monitored anesthesia care [MAC]) should be performed during stroke endovascular therapy. Both retrospective and prospective studies have shown that MAC has associated with better clinical outcomes.[54-56] However, other nonrandomized and randomized controlled trials did not show superiority of one method over the other.[57-60] A 2017 meta-analysis showed that there was no difference in GA versus non-GA in terms of neurological outcomes or 90-day mortality. There are advantages of both anesthesia techniques. General anesthesia provided a more secure airway and less patient movement. Monitored anesthesia care takes a shorter time for initiation, has a lower risk of pulmonary complications, and a neurological examination can be performed after endovascular treatment has been completed. Given the mixed evidence, the choice should be determined by patient and procedural factors and discussed with neurointerventionalist.[61]

Treatment of Large Core Strokes

Given that study cohorts in both DAWN and DEFUSE 3 had infract volume of less than 70 mL,[5,6] it is still undetermined what treatment should be offered to those with core volumes greater than 70 mL. Few studies have shown endovascular therapy has been beneficial for strokes with ischemic volume greater than 70 mL. Chen et al performed a retrospective review and stated that endovascular therapy performed within 6 hours of onset achieved higher reperfusion and recanalization rates compared to IV-tPA.[62] Gligen et al demonstrated similar results in younger patients with large MRI-DWI lesions.[63] Kaesmacher et al were able to show that mechanical thrombectomy in patients with Alberta Stroke Program Early CT Score of 0 to 5 were able to have successful reperfusion, with no increase in the rate of sICH.[64]

However, there has been new evidence recently that contradicts the benefits of endovascular therapy in large acute stroke. Sarraj et al pooled data from both the optimizing patient's selection for endovascular treatment in acute ischemic stroke (SELECT) and thrombectomy revascularization of large vessel occlusions in acute ischemic stroke (TREVO) trials and stratified the data by ischemic stroke volume. Larger ischemic volumes were associated with worse 90-day-modified Rankin scales, higher intracerebral hemorrhage rates, worse neurological status, and higher mortality rates, especially as the volume exceeded 100 mL. A reduction in positive outcome of 5% per hour and 27% per 10 mL of volume in large core stroke was shown.[65] With this information, there still needs to be a randomized controlled trial compared to medical management to determine whether endovascular therapy is beneficial in large volume acute ischemic stroke.

Future Research in Posterior Circulation Strokes

Research dealing with posterior circulation strokes has also been studied. Basilar artery thrombosis (BAT) has been the main focus in the posterior stroke field. There is a paucity of literature for the treatment of basilar artery thrombosis. Basilar artery thrombosis is associated with a high mortality rate when recanalization is not achieved.[66,67] The imaging evaluation for BAT follows that for anterior strokes in general with the caveat that MRI is the preferred imaging modality for the brain since posterior fossa produces streak artifacts that limit CT evaluation.[66] For arterial imaging, CTA is preferred over contrast MRI which is limited by breathing artifacts.[68]

There is variation in the time window for BAT treatment. The Madrid Stroke Network consensus protocol for treating BAT includes selection criteria of (1) confirmation of large vessel occlusion on CT angiography, (2) moderate-to-severe neurological deficit, and (3) $\leq$12 hours from symptom onset.[69] Additional centers use a time window of up to 24 hours after symptom onset due to collateral circulation and retrograde filling of the distal basilar artery that may still perfuse the brainstem.[70]

Although successful recanalization of the basilar artery can increase survival, it does not necessarily yield an improvement in disability-free outcomes.[71] In fact, basilar artery occlusion is associated with a 50% futile recanalization rate compared to 35% in anterior circulation thrombosis and is associated with longer procedure times and higher rates of complications compared to treating anterior circulation occlusions.[70] However, new research might show when mechanical thrombectomy in certain subtypes of BAT might have successful recanalization and clinical benefit, in particular those without vertebral artery occlusion.[72] Further advances in endovascular and imaging techniques for basilar artery thrombosis may improve outcome results relative to treating occlusions in the anterior circulation.[73]

Summary

Recent randomized controlled trials, such as DEFUSE-3 and DAWN with endovascular intervention and WAKE UP, MR WITNESS, and EXTEND with IV-tPA, have highlighted the significance of treatment of late acute ischemic stroke in patients 6 to 24 hours after symptom onset who show favorable imaging profiles.

Declaration of Conflicting Interests

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