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A Review of Acute Ischemic Stroke Imaging Applications in Patient Selection for Cerebral Thrombectomy

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Abstract

Before the introduction of modern treatments, acute ischemic stroke (AIS) resulted in 10% early mortality, around 50% of survivors left with moderate-to-severe neurologic deficits, and 25% left dependent on others. This drastically improved with the introduction of intravenous tissue plasminogen activators and later with endovascular treatment (EVT). Patient selection for EVT relies on dedicated multimodality neuroimaging conducted with four main goals – 1) exclude a hemorrhagic stroke and identify early ischemic changes, 2) identify a proximal large vessel occlusion, 3) determine the volume of 'ischemic core', and 4) determine the volume of 'ischemic penumbra'. This comparative narrative review aims to discuss in detail how different imaging modalities are used in the context of AIS to select patients for EVT. This includes computed tomography (CT) and magnetic resonance imaging (MRI), including their role in angiographic and perfusion imaging. Based on the success of EVT trials from 2015 and 2018, the updated American Heart Association - American Stroke Association guidelines state that non-contrast head CT and CT angiography are sufficient to identify patients who are fit to undergo EVT in the early window (<6 hours from onset of symptoms or last known normal). Additional perfusion imaging to evaluate the core, penumbra, and mismatch is recommended for selecting patients for EVT in the late window (6-24 hours from the onset of symptoms or last known well). However, the eligibility criteria from the DAWN and DEFUSE 3 trials should be strictly adhered to. It is also very likely for treatment guidelines to extend eligibility criteria soon based on the latest trials indicating that patients with large strokes also benefit from EVT with improved functional outcomes.

Keywords: Acute Ischemic Stroke; Cerebral Thrombectomy; Mortality; Intravenous tissue

INTRODUCTION

A stroke is a neurological deficit attributed to an acute focal injury of the central nervous system due to a vascular cause [1], The etiology of stroke is broadly classified as either ischemic or hemorrhagic. Most strokes are ischemic in nature, resulting from arterial occlusion causing reduced blood flow. Venous causes of ischemic stroke are much rarer and can be due to occlusion of cerebral veins or venous sinuses. Hemorrhagic strokes account for 10-40% of stroke presentations and are due to rupture of cerebral arteries [2,3], Hemorrhagic strokes are either intracerebral or subarachnoid in nature. According to the 2019 Global Burden of Diseases published in 2021, stroke remained the second leading cause of death worldwide and the third most common cause of death and disability combined. The incidence of ischemic strokes in 2019 was 7.63 million (62.4%), which was much higher than the incidence of hemorrhagic strokes (combined intracerebral and subarachnoid) which was 4.59 million (37.6%) [4].

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A typical presentation of an Acute Ischemic Stroke (AIS) includes the rapid onset of neurologic deficits localized to a single cerebral arterial vascular territory [5], Before the introduction of modern treatments that are available today, early mortality in AIS was reported to be 10% [6]. Additionally, among the survivors, around 50% were left with moderate-to-severe neurologic deficits, and 25% were left dependent on others [7]. In 1995, these trends saw a drastic change with immense improvement due to the introduction of intravenous alteplase [5,8]. In more recent times, the introduction of endovascular treatments (EVT) has radically altered the management strategies of many AIS patients [5].

Endovascular treatment (EVT) has now been established as a potent option for patients with AIS and large vessel occlusion (LVO) involving the anterior circulation. From the year 2015-2018, a total of 8 trials revolutionized AIS management by showing that EVT is an effective treatment for patients with AIS resulting from LVO. 6 trials in 2015 (MR CLEAN, ESCAPE, REVASCAT, EXTEND-IA, SWIFT PRIME, AND THRACE) proved EVT to be an effective treatment option for AIS patients presenting within 6 hours of symptom onset (early window) [9-14]. The number needed to treat and prevent disability in the context of anterior circulation large vessel occlusion with small-to-moderate strokes (core <50mls) and treated within 6 hours from symptom onset is 2.3 [15-17]. In 2018, 2 more successful trials (DAWN and DEFUSE 3), demonstrated that EVT is also an effective treatment option for AIS patients presenting up to 24 hours of symptom onset (late window) [18,19]. These results have led to widespread acceptance of EVT as a treatment option for AIS and LVO with changes in the management guidelines.

All 8 trials from 2015-2018 used a well-integrated and multimodal imaging approach in optimizing the selection of patients who would show benefit from an EVT. Neuroimaging plays a central and crucial role in establishing a diagnosis of AIS in patients presenting with sudden onset neurological deficits by ruling out hemorrhagic stroke and stroke mimics

such as seizures, syncope, transient global amnesia, complex migraines, etc. The ultimate goal of neuroimaging is to augment the selection of patients with AIS and LVO who would benefit from an EVT such as mechanical thrombectomy or clot retrieval.

In order to conduct this narrative review, a comprehensive search for literature was done on databases including PubMed, Science Direct, EBSCO, and MEDLINE by using the keywords – "Endovascular treatment trials", "EVT trials", "Ischemic stroke imaging", "CT stroke", "CTA stroke", "CTP stroke", "NCHCT stroke", "MRI stroke", "DWI stroke", "MRP stroke", and "MRA stroke". Relevant literature for the period of 1991 – 2022 was studied and included accordingly. Additionally, 8 EVT trials conducted during the period of 2015 - 2018 were included in this comparative and narrative review (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, EXTEND-IA, THRACE, DAWN, and DEFUSE-3).

CLINICAL SCORING SYSTEMS

NIHSS

The National Institute of Health Stroke Scale (NIHSS) is the most widely used impairment rating score in neurology and is also frequently used as an early secondary outcome measure in stroke trials [9-14,18-20]. The NIHSS measures neurological deficits rather than functional outcomes. The NIHSS is a 15-item neurological quantitative exam used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. Ratings for each item are scored on a 3- to 5-point scale, with 0 as normal. The total score ranges from 0 – 42, with higher scores indicating greater severity of stroke. The severity of stroke can be stratified from mild (NIHSS 0-5) to very severe (NIHSS ≥ 25) [21].The scale reflects cerebral dysfunction and is also responsive to meaningful clinical change [22]. NIHSS also holds a strong prognostic value for both short and long-term clinical outcomes [23-25].

Modified Rankin Scale (mRS)

The mRS is a clinician-reported hierarchical 7-level scale to measure global disability post ictus. It is one of the most widely employed clinical outcome scales in stroke trials. The scale ranges from grade 0 which denotes no symptoms at all to grade 5 denoting severe disability and grade 6 denoting a fatal outcome. The mRS can be performed rapidly and can be documented by individuals from broad training and professional backgrounds [26,27].

NEUROIMAGING IN AIS

Neuroimaging in AIS involves a multimodality imaging approach which involves parenchymal imaging to identify early ischemic changes and to rule out intracerebral hemorrhage (ICH), vascular imaging to evaluate the site of occlusion, vessel patency, and collateral status, and perfusion imaging to measure perfusion parameters and identify potentially salvageable brain tissue [28]. An integrated multimodality CT imaging approach with non-contrast head CT, CT angiography, and CT perfusion imaging is quick to perform and can be performed with almost all current scanners. Due to its wide availability, cost-effectiveness, and faster speed of acquisition, CT protocols are preferred over MR-based imaging protocols and are generally the main modality used in most stroke centers. Like CT protocols, MRI protocol of stroke also involves a multimodality approach involving DWI to detect Early Ischemic Changes (EICs) and delineate the ischemic core, fluid-attenuated inversion-recovery (FLAIR) and gradient-echo (GRE) to detect ICH, vascular imaging in the form of MRA, and MRP imaging to determine the penumbral volume. However, MRI protocols hold certain disadvantages mainly low availability, longer acquisition times leading to delayed workflow, and patients with uncertainty as to whether they have compatible prosthesis. The general consensus is that MRI should only be used for EVT selection in institutions or settings where speed and triaging efficiency can be achieved which is comparable to CT-based protocols [28].

The four main goals of conducting multimodality neuroimaging are as follows – 1) To exclude a hemorrhagic stroke and identify EICs, 2) To identify a proximal LVO, 3) Determine the volume of 'ischemic core', and 4) Determine the volume of 'ischemic penumbra'. This comparative narrative review will discuss in detail which imaging modalities are used to accomplish each of these goals of neuroimaging in patients of AIS.

Excluding a hemorrhagic stroke and identifying EICs

CT Imaging: The presence of an acute ICH is an absolute contraindication to intravenous tissue plasminogen activator (IV-tPA) therapy. A non-contrast head CT (NCHCT) is generally the imaging modality of choice to rule out an ICH in a patient suspected of having an AIS [29]. NCHCT is inarguably the imaging study of choice in the initial evaluation of patients with a suspected AIS and is performed for all patients. Not only is NCHCT widely available and inexpensive, but also rapidly obtained for evaluation. Clinically, the presentation of an AIS and ICH can be indistinguishable. NCHCT plays a pivotal role in ruling out ICH which is an absolute contraindication to IV-tPA or EVT [30,31]. In addition to ruling out an acute ICH, NCHCT is also serves to detect early ischemic changes (EICs), chronic infarcts, or the hyperdense vessel sign. EICs on NCHCT can include loss of grey-white differentiation, cortical swelling, or mass effect [32,33]. With the progression of the infarct, it becomes irreversible and cytotoxic edema ensues. At this point, the infarct starts to appear as a more pronounced hypodensity [32]. The presence of an obvious, well-established large hypodense infarct (> 1/3rd of the MCA territory or 100 mL) is also a relative contraindication of IV-tPA therapy [29].The hyperdense vessel sign is defined as a focal hyperdensity within an artery compared to the normal appearance of an artery. This sign has high specificity (90-100%) albeit low sensitivity and can help identify a proximal thrombus and clot burden. It is often one of the earliest signs of an AIS on NCHCT[34,35]. To determine the extent of EICs on NCHCT, the Alberta Stroke Program Early CT Score (ASPECTS) is often used. ASPECTS is a CT scoring system that quantitatively measures the extent of EICs in anterior circulation hyperacute ischemic strokes [36]. It involves a segmental assessment of the MCA vascular territory, and 1 point is deducted from the initial total score of 10 for every region showing EICs. The 10 regions which are assessed in ASPECTS include the caudate, putamen, internal capsule, insular cortex, and M1-M6 (six lobar parenchymal regions). This score has been applied in imaging selection for EVTs to isolate patients with the greatest extent of ischemic damage, in whom reperfusion therapies would yield no benefit or even be potentially harmful [37]. ASPECTS has been recognized as a key selection criterion in the updated American Heart Association (AHA) guidelines on the management of acute stroke, where EVT in patients with baseline ASPECTS of ≥ 6 is recommended [38]. Although ASPECTS has successfully been implemented in several clinical trials, there remains some uncertainty due to variations in inter-reader agreements [39-41].

Although not yet established in treatment guidelines, the latest trials on cerebral thrombectomy indicate that patients with ASPECT score 3-5 also benefit from the procedure with improved functional outcomes [42-45].

MR imaging: FLAIR and GRE imaging has excellent accuracy in the detection of acute ICH, comparable to that of NCHCT [46,47]. MRI appearance of hemorrhage changes as the hematoma evolves over time. Hyperacute hemorrhage (< 24 hours) contains oxyhemoglobin and appears T1 isointense and T2 bright, acute hemorrhage (1-3 days) contains deoxyhemoglobin and appears T1 isointense and T2 dark, early subacute hemorrhage (> 3 days) contains methemoglobin and appears T1 bright and T2 dark, and chronic hemorrhage (>14 days) contains hemosiderin and appears T1 and T2 dark [32]. Due to the suppression of the CSF signal, subarachnoid and subdural hemorrhages can be readily identified on the FLAIR sequence. On the post-contrast FLAIR sequence,

the HARM sign (hyperintense acute reperfusion marker) represents a disrupted blood-brain barrier and is associated with an increased risk of hemorrhage after reperfusion therapies [48].

The biggest advantage and greatest value of MRI lies in the diffusion-weighted imaging (DWI) sequence which is the most sensitive modality for evaluating EICs (unlike CT which is specific but insensitive) and assessing the ischemic core [28,29]. DWI has a reported sensitivity of 90% (95% CI: 87.9% - 92.6%), specificity of 97% (95% CI: 91.8% - 99%), and accuracy of 95% in the detection of the ischemic core (irreversibly infarcted brain tissue) [49]. DWI is a method of signal contrast generation based on the Brownian motion of water in tissue. Apparent diffusion coefficient (ADC) maps are very useful in differentiating true restricted diffusion from T2 shine-through. True restricted diffusion will be visible as DWI bright, ADC dark, and T2 bright, whereas T2 shine-through will appear as DWI bright, ADC bright, and T2 bright [29,32]. The ASPECTS has also been applied to DWI which appears to be a reliable tool for predicting treatment outcomes in AIS patients. Mitomi et al. [50], in their comparative study between CT and DWI findings in AIS patients within 3 hours of symptom onset showed a higher detection rate of ischemia with DWI-ASPECTS compared to CT-ASPECTS. Other studies have also reported on better detection of ischemic lesions by DWI [51-54]. In contrast, a previous study reported on similar detection rates of ischemia with DWI- and CT-ASPECTS [55]. A higher rate of detection of ischemia with DWI can be attributed to a couple of factors. DWI has the ability to visualize ischemic changes earlier than CT [56]. Animal models have shown intensity changes apparent on DWI after only a few seconds of vessel occlusion [57]. Additionally, DWI's superior capability of detection of ischemia can be attributed to ASPECT's focus on anterior circulation [58,59]. A limitation of DWI-ASPECTS is the overestimation in the penetrating branch territory of MCA. ASPECTS regions such as the caudate, internal capsule, lentiform nucleus, and insular ribbon are small-volume brain structures, thus, a small-volume lesion involving these structures can lead to a low score [60].

Imaging data from DWI combined with FLAIR also serves to estimate the timing of ischemic onset, making it suitable to guide management for wake-up strokes. A DWI-FLAIR mismatch has been identified as a marker of a stroke that is <4.5hrs from onset [61].

Susceptibility weighted imaging (SWI) demonstrates acute intra-arterial thrombus as low signal referred to as the 'susceptibility sign', and FLAIR demonstrates the same as a 'hyperintensity sign'. These are equivalent to the 'hyperdense sign' described in CT scans. The 'susceptibility sign' on SWI for MCA occlusions has the highest sensitivity compared to the other modalities [62].

Identifying a proximal Large Vessel Occlusion (LVO)

The majority of the morbidity and mortality from stroke is a result of a large-vessel proximal occlusion of the middle cerebral artery (MCA) or other proximal Circle of Willis arteries. Thus, it is crucial to identify the site of LVO as a target for EVT. CT angiography (CTA) or MR angiography (MRA) are the imaging modalities used to identify the site of proximal LVO. CTA is utilized more often than MRA [29].

CT angiography: In potential candidates for EVT, CT angiography (CTA) is recommended for the evaluation of both intra- and extra-cranial arteries during the initial imaging evaluation [16]. CTA is a fast and reliable method for evaluating intracranial occlusive disease. The sensitivity and specificity of CTA are reported to be up to 100% in large vessel intracranial occlusive disease [63]. This makes CTA an excellent modality to identify the location of proximal LVO as a target for EVT. CTA as a vascular imaging modality was used in all of the 8 trials on EVT conducted between 2015 and 2018 [9-14,18-19]. Maximum intensity projection (MIP) and 3D reconstructions are used to detect more distal sites of stenosis or occlusion, clot burden, and most importantly, the leptomeningeal collateral status [64,65].

Clot burden is an important measure of CTA. It can predict the patients' outcome of IV-tPA therapy. Patients with LVO and a clot length of > 8 mm are unlikely to be successfully recanalized with IV-tPA alone and may potentially be good candidates for EVT [29, 65,66].

Another measure of CTA that can help distinguish patients who are most likely to benefit from EVT is the leptomeningeal collateral status [29]. It has been reported that patients with a proximal LVO and good collateral status tend to have a smaller volume of the ischemic core and a larger volume of penumbra (potentially salvageable tissue). Whereas patients with a proximal LVO and a poor collateral status tend to have a larger volume of the ischemic core and a smaller volume of salvageable tissue[64].Thus, good leptomeningeal collateral status can be a predictor of a beneficial clinical outcome in an AIS patient after EVT. The leptomeningeal collateral status on CTA can be stratified into 3 categories – robust collaterals (i.e., symmetric), poor collaterals (absent collateralization in more than 30-50% of territory at risk), and intermediate status. Patients with robust leptomeningeal collaterals are more likely to have a good beneficial outcome after EVT[29,67]. Two other scales used to stratify collateral status are the Tan score (0 = no collaterals, 1 = <50% collateralization of the territory at risk, 2 = ≥50% but <100% collateralization, and 3 = 100% collateralization) [68], and the Maas scale (1 = absent, 2 = less than the contralateral side, 3 = equal to the contralateral side, 4 = more than the contralateral side, and 5 = exuberant) [69].

MR DWI is the modality that is most accurately able to calculate the volume of the ischemic core. Thus, in cases where DWI is unavailable or contraindicated, leptomeningeal collateral status can help predict the potential outcome of performing a recanalizing procedure in a patient with AIS.

MR angiography: Although MR angiography (MRA) is a robust tool for the detection of proximal LVO, it is much more time-consuming when compared to CTA and often not available in an emergent setting. Therefore, the application of MRA becomes apparent when CTA cannot be performed due to contrast allergy or renal failure [32]. MRA of the head and neck can be performed with or without the use of a contrast agent. In patients with renal failure or patients on dialysis, MRA can be obtained by using the time-of-flight technique due to the concern of contrast retention [32].The time-of-flight MRA technique utilizes a vascular signal that is flow-dependent on the direction and velocity of the blood. However, this technique has the limitations of being prone to artifacts, overestimation of the degree of stenosis, and inaccuracy in identifying distal occlusions. It is important to note that despite its limitations, MRA has very high sensitivity (87%) and specificity (98%) in the detection of occlusive disease [70].

Determining the volume of 'ischemic core' and 'ischemic penumbra'

Ischemic core is defined as the volume of brain tissue that is irreversibly damaged. The volume of the ischemic core is crucial because several studies have reported that beyond a certain volume (> 70 mL) of the core, EVT is unlikely to produce a beneficial clinical outcome [71,72]. In fact, patients with an ischemic core of > 70 mL are at a higher risk of intraparenchymal hemorrhage after a reperfusion procedure. Perfusion imaging including CT perfusion (CTP) or MR perfusion (MRP) is often used in determining the volume of the ischemic core. MR diffusion-weighted imaging (MR DWI) and corresponding ADC maps are also highly useful in calculating the size and volume of the ischemic core [29].

The ischemic penumbra is defined as the volume of tissue at risk of irreversible injury which can be potentially salvageable by reperfusion therapies. When there is a substantial lack of volume of such salvageable tissue, the risks of performing the EVT procedure outweigh the benefits. Perfusion imaging (CTP or MRP) is used to calculate the volume of

penumbral tissue [29].

CT perfusion imaging: CT perfusion (CTP) imaging is used to measure the perfusion of cerebral tissue. The technique involves the administration of an IV bolus of iodinated contrast followed by repeated CT acquisitions over the same region of the brain over a period. This allows the visualization of the transit of contrast into the arteries, capillaries, parenchyma, and veins. Subsequently, CTP measures are calculated. Commonly derived CTP maps include cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time-to-maximum of the tissue residue function (Tmax) [32,73]. CBF and CBV changes relative to the contralateral hemisphere are used to measure the ischemic core and MTT and Tmax are used to measure the penumbra. Although many variations exist, the most commonly used threshold to define the ischemic core is a relative reduction of 30% - 45% in the CBF, and a Tmax > 6 seconds is used to define penumbral predictions [74-77].The penumbral volume divided by the ischemic core volume gives a mismatch ratio. These measurements are automated and performed by software packages such as RAPID, Olea, GE, Philips, Siemens Syngo, and MIStar [73]. The EVT trials that used CTP as a parameter in selecting patients for EVT also used automated software to derive their perfusion parameters.

CTA source images can be used to detect infarcted tissue in the brain. Hypoenhancement of a 40/40 window distal to the LVO indicates hypoperfused brain tissue that will eventually be irreversibly damaged without reperfusion [78]. Kamalian et al. [29], reported on a simplified scoring system that combines the size of CTA hypodensity from source images and leptomeningeal collateral status that can provide an accurate estimation of the ischemic core volume. This method can be beneficial to primary stroke centers in decision-making regarding the transfer of patients [29].

MR perfusion imaging

Magnetic resonance perfusion (MRP) is similar to CTP as it produces perfusion maps based on the CBF, CBV, Tmax, and MTT parameters. MRP, however, can also be obtained without the need for iodinated contrast by using arterial spin labeling. One advantage of MRI protocols over CT protocols is that due to the accuracy of DWI in estimating ischemic core, MRP can solely be used to estimate the penumbra by using Tmax > 6 seconds [79].

As mentioned before, MR-DWI is the modality that is most accurately able to calculate the volume of the ischemic core, which is an important marker in predicting the likelihood of good outcomes in AIS patients. The ischemic core volume on DWI can be estimated by multiplying the largest cross-sectional dimensions on axial, sagittal, and coronal reconstructed images and dividing the product by 2 (length x width x height/2). Patients with the potential to derive the greatest benefit from recanalization procedures usually have a core volume of < 70 mL at presentation. Those with large initial core volumes (>100 mL) have been traditionally regarded as unlikely to benefit from EVT and at risk of hemorrhage after reperfusion [29,80,81]. However, the latest trials on cerebral thrombectomy indicate that even patients with ASPECT scores 3-5 can benefit from the procedure, with improved functional outcomes [42,45].

CURRENT EVIDENCE ON IMAGING-BASED SELECTION OF AIS PATIENTS FOR EVT

The American Heart Association-American Stroke Association (AHA-ASA) guidelines state that any AIS patient with significant neurologic deficits (NIHSS ≥ 6) presenting with a LVO within 24 hours of symptom onset may be a potential candidate for EVT depending upon their imaging findings [82]. Thus the primary purpose of imaging in AIS patient selection for EVT is to identify patients in whom the benefits of performing EVT outweigh the risks.

The six 2015 EVT trials established the role of EVT in AIS patients who present within 6 hours of symptom onset or last known well (early window) [9-14]. and the two 2018 trials established the role of EVT in AIS patients who present within 6-24 hours of symptom onset or last known well [18,19]. Table 1 shows a summary of all EVT trials from 2015 and 2018.

All 6 trials from 2015 showed the benefit of EVT after IV-tPA compared to IV-tPA alone [9–14].The 2015 trials The Mr CLEAN, ESCAPE, and THRACE proved that in patients with suspected proximal LVO presenting within 6 hours of symptom onset or last known well, NCHCT and CTA can provide sufficient imaging insight to decide regarding EVT candidacy of AIS patients [9,10,14]. Among all EVT trials, the use of vascular imaging (CTA or MRA) to identify LVO was common which was defined as intracranial carotid or M1 occlusion in all of the trials. SWIFT PRIME and EXTEND-IA also used M2 occlusion as inclusion criteria and MR CLEAN included both anterior cerebral artery and M2 occlusions in their criteria [12,13]. MR CLEAN trial suggested a role for pial collateral status assessment in determining which patients are likely to benefit from EVT [9]. The ESCAPE trial used multiphasic CTA to assess the leptomeningeal collateral status and used the threshold of ≥ 50% collateralization of MCA pial circulation to dichotomize findings into good or moderate and poor or absent [10]. They used this criterion to enroll patients into the EVT group and showed EVT benefits over medical therapy alone. It is well-established that patients with poor collateral status are fast progressors (faster rate of infarct growth and progression), whereas patients with good collateral status are slow progressors (able to sustain the ischemic bed for longer) [28].

MR CLEAN, ESCAPE, and THRACE trials of 2015 proved that in AIS patients with LVO presenting within 6 hours of onset, NCHCT and CTA are enough to make a decision on enrolling patients into the EVT group without the need for any additional imaging [9,10,14]. MR CLEAN and THRACE used NCHCT to define the core as 1/3rd of the MCA territory without using ASPECTS to evaluate EICs [9,14]. Whereas ESCAPE used an ASPECTS of ≥ 6 to define the EICs [10]. Therefore, patients with intracranial occlusive disease and an absence of a large infarct core on NCHCT with an ASPECTS ≥ 6 are considered eligible candidates for EVT. If an MRI protocol is utilized instead of a CT protocol, a DWI ASPECTS of ≥ 6 and vascular imaging with MRA may be used to establish eligibility for EVT [28]. For example, SWIFT PRIME used the criteria of CT or MRI ASPECTS ≥ 6 and REVASCAT used the criteria of CT ASPECTS ≥ 7 or MRI ASPECTS ≥ 6 to determine patients that are safe to go under EVT [11,12]. The only trial that only used MRI to stratify patients was THRACE [14].

Although these trials established the fact that NCHCT and CTA are sufficient to stratify patients into who may benefit from EVT and who may not, it is worth noting that several of the early window trials of 2015 also utilized additional imaging in the form of perfusion imaging (CTP or MRP) to establish candidacy for EVT. The only trial that used perfusion imaging (CTP) In all patients to enroll them into the EVT category was EXTEND-IA by defining an ischemic core of <70 mL as eligibility for EVT [13]. SWIFT PRIME used CTP to define a core volume of <50 mL initially to enroll patients into the EVT subset but later switched to ASPECTS ≥ 6 on CT/MRI [12]. Hence, these trials proved that additional imaging other than CT/MR DWI and vascular imaging (CTA or MRA) is not necessary in AIS patients presenting within the early window (within 6 hours of last known well).

The drawbacks of performing additional imaging such as perfusion imaging in patients presenting in the early window are the potential for delays in treatment and inappropriate exclusion of patients who would in reality benefit from EVT [28,81]. The 2019 updated AHA-ASA guidelines for mechanical thrombectomy also state that the selection of patients who present within 6 hours of last known well with LVO and ASPECTS ≥6, only require CT and CTA or MRI and MRA, and additional perfusion imaging is not indicated in the early window [82].

Table 1: Summary of the eight EVT trials with imaging modalities and criteria used and other attributes

	MR CLEAN [9]	ESCAPE [10]	REVASCAT [11]	SWIFT PRIME [12]	EXTEND-IA[13]	THRACE [14]	DAWN [18]	DEFUSE 3 [19]
Year	2015	2015	2015	2015	2015	2015	2018	2018
Number of patients	500	315	206	196	70	414	206	182
Imaging modalities used	CT CTA	CT multiphasic CTA	CT, MRI CTA or MRA CTP	CT, MRI CTA or MRA CTP or MRP	CT CTA CTP	CT, MRI CTA or MRA	CT, MRI CTA or MRA CTP	CT, MRI CTA or MRA CTP
Criteria for EICs and/or ischemic core	1/3rd of MCA territory at risk	ASPECTS ≥ 6	CT ASPECTS ≥ 7 MRI ASPECTS ≥ 6	CT/MRI ASPECTS ≥ 6	Ischemic core volume < 70 mL using CTP Absolute mismatch volume > 10 mL Mismatch ratio > 1.2	1/3rd of MCA territory at risk	Core ≤ 20 mL if age > 80 y Core ≤ 30 mL if age < 80 y and NIHSS 10-20 Core ≤ 50 mL if age < 80 y and NIHSS > 20	Volume of ischemic core ≤ 70 mL Mismatch ≥ 15 mL Mismatch ratio ≥ 1.8
Perfusion imaging criteria	-	-	CTP-CBV ASPECTS, or CTP-SI ASPECTS (if >4.5 h from onset)	Volume of ischemic core <50 mL Mismatch >1.8		-	Core at MRI: ADC <620 x 10^{-3} mm^2/sec Core at CTP: rCBF < 30%	Core at MRI: ADC <620 x 10^{-3} mm^2/sec Core at CTP: rCBF < 30% Penumbra on CTP: Tmax > 6 sec
Time frame	6 hours	< 12 hours	< 8 hours	6 hours	6 hours	5 hours	6-24 hours	6-16 hours
90-day functional independence measured by mRS after EVT (EVT vs control)	32.6% vs 22.1%[1]	53.0% vs 29.3%*	43.7% vs 28.2%*	60.2% vs 35.5%*	71.4% vs 40.0%*	53% vs 42%*	49% vs 13%*	44.6% vs 16.7%*

[1]Statistically significant

CTA = CT Angiography; MRA = MR Angiography; CTP = CT Perfusion; MRP = MR Perfusion; EIC = Early Ischemic Change; MCA = Middle Cerebral Artery; ASPECTS = Alberta Stroke Program Early CT Score; NIHSS = National Institute of Health Stroke Scale; CBV = Cerebral Blood Volume; SI = Source Image; ADC = Apparent Diffusion Coefficient; rCBF = relative Cerebral Blood Flow; mRS = modified Rankin Scale; EVT = Endovascular Treatment

While perfusion imaging is not indicated in patients with AIS presenting during the early window, perfusion imaging has proven to provide helpful additional insight regarding the ischemic core, salvageable penumbra, and mismatch in patients with AIS presenting in the late window (6-24 since the onset of symptoms or last known well). The recent success of the 2018 late window EVT trials DAWN and DEFUSE 3 highlighted the importance of perfusion imaging in routine clinical practice [18,19]. The DAWN trial aimed to determine the EVT candidacy between 6-24 hours of symptom onset by using the NIHSS score and perfusion imaging (volume of the ischemic core using CTP or MRP of ≤50 mL) [18]. DEFUSE 3 aimed to determine the EVT candidacy of patients between 6-16 hours of symptom onset by using perfusion core mismatch and ischemic core volume of ≤ 70 mL and the ratio of the ischemic tissue volume on perfusion imaging to infarct volume was ≥ 1.8 [19]. Clinical deficits were not used as an inclusion criterion in DEFUSE 3. Both DAWN and DEFUSE 3 utilized the thresholds of CBF < 30% for core predictions and Tmax > 6 seconds for penumbral predictions [18,19]. These trials successfully showed that with perfusion imaging selection, AIS patients can safely be treated with EVT up to 24 hours after the onset of symptoms. The DAWN trial was able to successfully demonstrate an overall benefit in functional outcome at 90 days in the EVT treatment group (mRS score 0–2, 49% functional independence in the treatment group versus 13% in control) [18]. Similarly, the DEFUSE 3 trial demonstrated a benefit in functional outcome at 90 days in the EVT treatment group (mRS score 0–2, 44.6% functional independence in the treatment group versus 16.7% in control) [19]. Thus, the updated 2019 AHA-ASA guidelines state that when selecting patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP or DW-MRI, with or without MRI perfusion, is recommended to aid in patient selection for mechanical thrombectomy, but only when patients meet other eligibility criteria from one of the randomized control trials (RCTs) that showed benefit from EVT in this extended time window [81]. The eligibility criteria for DAWN and DEFUSE 3 is summarized in Table 1.

CONCLUSION

A well-integrated, advanced, and multimodal imaging protocol plays a central and crucial role in the management of AIS by guiding the selection of patients for endovascular treatment. Based on the success of the EVT trials from 2015 and 2018, the updated AHA-ASA guidelines state that NCHCT and CTA are sufficient to identify patients who are fit to undergo EVT in the early window (<6 hours from onset of symptoms or last known normal). Additional perfusion imaging to evaluate the core, penumbra, and mismatch is recommended in selecting patients for EVT in the late window (6-24 hours from the onset of symptoms or last known well), According to the aforementioned guidelines the eligibility criteria from the DAWN and DEFUSE 3 trials should be strictly adhered to. It is also very likely for treatment guidelines to extend eligibility criteria based on the latest trials indicating that patients with ASPECT scores 3-5 also benefit from the procedure with improved functional outcomes.

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