Acute Ischemic Stroke: A Review of Imaging, Patient Selection, and Management in the Endovascular Era. Part I: Initial Management and Imaging

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Abstract

Till recently, the mainstay of management of acute ischemic stroke (AIS) has been intravenous thrombolysis. However, response to treatment and outcomes in the presence of a large vessel occlusion (LVO) were largely suboptimal. Endovascular thrombectomy techniques with stentrievers and aspiration catheters have revolutionized stroke treatment significantly, improving outcomes in this once untreatable disease. The interventional radiologist must play an active role in the stroke team in streamlining imaging as well as endovascular management. The focus of this review article is on initial management and imaging. Initial measures consist of patient resuscitation, basic investigations and assessment of stroke severity using the National Institutes of Health Stroke Scale (NIHSS), all of which have therapeutic and prognostic implications to be considered by the neurointerventionist. Imaging must aim to be swift and efficient. Choice of a modality must be based on available infrastructure as well as clinical-radiologic factors such as the time since ictus or posterior circulation involvement. Computed tomography (CT) is the preferred modality for its speed, whereas magnetic resonance imaging (MRI) remains the gold standard problem solving technique for detection of stroke. Exclusion of hemorrhagic stroke and other stroke mimics is the first objective. Thereafter, imaging is targeted toward assessing the parenchyma and vasculature. Defining the core and penumbra is the most important goal of parenchymal imaging. The core may be defined by the presence of early ischemic changes on CT, CT angiographic source images, or diffusion restriction on MRI. The penumbra is approximated by collateral status or perfusion methods. The prime directive of vascular imaging, either CT or magnetic resonance angiography (MRA) is to establish the presence of an LVO. Once confirmed, the decision for thrombolysis and/or thrombectomy is based on clinical and imaging criteria, the most ideal being that of a moderately severe stroke with a small core and LVO on imaging.

Keywords
- stroke
- mechanical thrombectomy
- neurointervention

Introduction

Acute ischemic stroke (AIS) has now become a treatable disease owing to a paradigm shift particularly in the endovascular treatment (EVT) of large vessel occlusions (LVOs). Ischemic stroke constitutes a major public health problem in India with higher rates of incidence and prevalence than developed countries.[1,2] Emergent LVOs (ELVO) cause approximately 20 to 40% of ischemic strokes but account disproportionately for the majority of stroke-related morbidity and mortality.[3] Multiple recent randomized controlled trials (RCTs) strongly support the natural idea that recanalization

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of the occlusion and resulting tissue reperfusion translate into improved clinical outcomes.

Clinical Presentation and Grading

Epidemiologically, a stroke is defined by the evidence of rapid development of focal or global disturbance of cerebral function.[4] The presence of motor or sensory impairment, dys/aphasia, hemianopia, gaze palsies, ataxia, apraxia, and dysphagia either alone or in combination are considered definite clinical evidence of focal neurologic deficit. Posterior circulation strokes are more likely to be preceded by transient ischemic attacks (TIAs) or warning strokes and the presence of an associated headache, usually ipsilateral to the infarct. Ocular motor abnormalities such as gaze palsies, nystagmus, ocular tilt reactions, or Horner's syndrome as well as cerebellar signs, acute unilateral deafness, or somnolence also point toward a posterior circulation territory stroke.

The National Institutes of Health Stroke Scale (NIHSS) is a clinical assessment tool that allows quantitative grading of stroke severity and thereby help in determining appropriate treatment and predict patient outcome.[5] The scale consists of 15 items graded from 0 to between 3 and 5 grades with 0 being normal and 42 being comatose and quadriplegic. It takes less than 10 minutes to complete at the bedside and has been proven to be reliable. Minor, moderate, and severe strokes are classified as NIHSS < 6, 6–25, and > 25, respectively.[6]

Prehospital Stroke Management

As indicated by the "time is brain" hypothesis, the ictus to treatment time needs to be as short as possible.[7,8] This is facilitated by prompt diagnosis and early recanalization, and is attained by streamlining all links in the prehospital chain of treatment. Sequentially, three major points of contact are present.[9]

At the level of the *public*, the major hindrance to stroke treatment is the lack of awareness of stroke symptoms. Public education programs and the World Health Organization (WHO)–endorsed FAST (Face drooping, Arm weakness, Speech difficulty, Time to call emergency) acronym reminds the general populace of the urgency of stroke treatment.[10] BE-FAST is a more recent acronym that includes Balance and Eyes to increase comprehensive recognition of stroke symptoms.[11]

At the level of the *dispatcher*, the DIASE (Dispatcher Identification Algorithm for Stroke Emergencies) is an algorithm that allows for identification of a stroke at the first phone call from the patient's bystander.[12] The algorithm allows for recognition of typical and atypical presentation of strokes and allows rapid dispatch of the ambulance team.

Time in transit in an ambulance represents the third point of management. A mobile stroke unit (MSU) is a specialized ambulance with computed tomography (CT) and laboratory facilities dedicated to meet the two essential criteria for intravenous (IV) thrombolytic (IVT) initiation: ruling out of an intracranial hemorrhage and checking for coagulopathies. In remote or rural areas where such an MSU may not be an economically viable proposition, a "greet and meet" system of a conventional ambulance traveling to a central stroke ambulance may be a more efficient and cost-effective option. Conversely, in urban areas with a high population density and poor ground level infrastructure, a dedicated helicopter may be used for rapid transit to a stroke center. This "helistroke" option is viable particularly if the incidence of strokes is high.[9]

The time during transit can also be efficiently utilized for initial stroke triage and treatment. Telestroke, the use of telecommunications to assess stroke patients, is now a viable option since the availability of fast live video streaming speeds using 4G mobile technology. Because up to 30% of stroke calls can be a mimic, the Telestroke Mimic (TM) score consisting of six major determinants (age, atrial fibrillation, hypertension, seizure, facial weakness, and NIHSS > 14) can be used to determine the likelihood of stroke.[13] Telemedicine can also be used to assess NIHSS.

Three models exist for transit with varying aims: The "standard care" model is the baseline model that presumes a conventional ambulance with only first aid administered in transit and all workup and treatment being done in-hospital. The "freezing concept" involves the freezing of the penumbra by the administration of magnesium sulfate. The neuroprotectant effects of Magsulf are most evident either within the golden hour (60–90 minutes) or even better the diamond half hour and rapidly becomes deficient thereafter. Freezing the penumbra is one of the frontiers of ongoing research in an effort to increase the number of patients eligible for IVT and EVT.[14] The "Ambulysis concept" involves in-transit workup and imaging and initiation of bridging IVT prior to transfer for a mechanical thrombectomy.[9]

It is important that the patient be referred to an appropriate hospital. Hospitals that aim to be stroke centers must have a written protocol for stroke evaluation and triage and have an administrator for stroke who oversees policies and procedures, can administer thrombolytics, and have round the clock neurointerventional and neurosurgical expertise. The American Heart Association (AHA) classifies such centers as *primary*, *comprehensive*, or *acute stroke-ready hospital* depending on the satisfaction of various criteria.[6] The drip n' ship model consists of transport to a primary stroke center where IVT may be initiated and then further transfer to an endovascular ready comprehensive stroke center (CSC). The mothership model requires transport directly to the CSC with or without ambulysis.[15]

In-hospital Management

Once in the hospital, the AHA and other societies have guidelines for appropriate time periods for physician evaluation, imaging, and treatment (►**Table 1**).[16,17] The primary aim of hospital treatment is to initiate thrombolysis as early as possible. A rapid assessment of the ABCs including saturation, general physical evaluation, and stroke assessment must be done by either the emergency or stroke physician. Premorbid illnesses, risk factors, and functional status must be enquired as these are factors in patient selection.[18]

Only a few investigations are considered necessary. Those with a near immediate report such as blood sugars and electrocardiogram (ECG) are reasonable to conduct. However,

Table 1 Time–based limits for management of AIS

Action	Time
Door to physician	≤ 10 min
Door to stroke team	≤ 15 min
Door to CT initiation	≤ 25 min
Door to CT interpretation (≥ 50% compliance)	≤ 45 min
Door to needle (≥ 80% compliance)	≤ 60 min
Picture (imaging) to puncture	< 60 min (ESCAPE) < 70 min (max < 90 minutes) (SWIFT PRIME) < 110 min, high-volume centers < 50 min (75% patients—2018 Multisociety Quality Improvement guidelines)
Door to stroke unit admission	≤ 3 h

Abbreviations: AIS, acute ischemic stroke; CT, computed tomography; ESCAPE, SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment.

blood samples may be collected for other investigations such as blood counts, coagulation profile, serum electrolytes, renal function tests, and cardiac ischemic markers while treatment is simultaneously performed. It is reasonable to carry out a contrast examination without the serum creatinine report.[19] An IV-line insertion is necessary and may be performed during this sample collection.[6,16]

Supportive measures involve the supplemental oxygen if the saturation is < 94%, management of raised sugars, making sure to avoid glucose containing solutions in such cases, and the reduction in blood pressures if > 185/110 mm Hg systolic and diastolic respectively. IV antihypertensives such as labetalol or nicardipine are preferred. Maintain a nil per oral status.[6,16] If imaging has not yet been performed in transit, this becomes the next step.

Imaging

The Relevance of the Zones of Ischemia

Acute ischemic stroke consists of several zones, each with its own importance and therapeutic implications (►**Fig. 1**). These zones are defined based on their regional cerebral blood flow (rCBF).[20] The rCBF of normal brain parenchyma ranges between 60 and 100 mL/100 g/min. *Ischemia* begins at a threshold of 22 mL/100 g/min. Tissues with drastically reduced CBF values of < 10 mL/100 g/min form the *ischemic core* and do not recover even with treatment. If revascularized, they are at high risk of hemorrhagic reperfusion injury, thereby contraindicating treatment of large core strokes. Tissues with an rCBF between 10 and 22 mL/100 g/min represent the *ischemic penumbra*. The penumbral tissue is symptomatic (i.e., manifest with a functional deficit) and cannot be differentiated clinically from the core. Successful revascularization results in reversal back to functional tissue whereas failure leads to rapid recruitment into the core. The delineation of the penumbra is the holy grail of stroke imaging with the aim of achieving safe reperfusion. Finally, rCBF reductions in the gray zone between 60 and 22 mL/100 g/min represent *oligemia*. Oligemic tissues remain functional, do not undergo recruitment into the core, and remain viable even without recanalization. Treatment aimed at these areas is thus unnecessary, emphasizing the importance of differentiating these areas from the salvageable penumbra at imaging.[20]

The Basic Necessities of Imaging

The aim of imaging in stroke is twofold: to assess patients in whom reperfusion therapy is useful and to exclude those in which it is futile or even endangering. Indirectly, imaging also provides a window into prognostication.

Computed tomography is the recommended modality by the AHA as it is the fastest and most cost-effective modality.[6] Magnetic resonance imaging (MRI), particularly diffusion-weighted imaging (DWI), is more sensitive, but its practicality in terms of cost and scanning times are hindrances in its universal utilization.

The first goal of imaging is to rule out intracranial hemorrhage as the evaluation and management are completely different and IVT is contraindicated. Imaging strategies in ischemic stroke can then be directed toward four objectives alliterated by the four Ps: *p*arenchyma, *p*ipes, *p*erfusion, and *p*enumbra.[21]

Parenchyma: Assessing the Core

Measurement of the ischemic core is important for both prognosis and therapy.

Computed tomography: Always use sequential (not spiral) acquisition with true axial reconstructions.[22] Infarctions can present in basically three stages of evolution: early ischemic changes (EICs), evolving infarcts, and established infarcts.[23] *EIC* are fundamentally an early stage of cytotoxic edema and are characterized by loss of gray-white differentiation (GWD). These are best viewed at a high contrast stroke window (centered at 32 HU with a width of 8 HU) that exaggerates subtle findings increasing sensitivity from 57 to 71%. A practical approach to windowing is to scroll to the ganglionic level and manually adjust window the image until the GWD is most well delineated on the expected normal side. Several named signs have been developed to recognize specific regions of EIC (►**Table 2**). *Established infarcts* appear as a definite area of hypodensity relative to the adjacent parenchyma whereas *evolving infarcts* appear as a more subtle hypodensity. These changes all represent irreversibly damaged tissue. It is important to note that the extent of EIC, not the degree of hypodensity, plays a role in prognostication and treatment decision.

Once the signs of a stroke have been established, the next step is to quantify the degree of territorial loss. Previously, involvement of more than one-third of the MCA territory was considered a contraindication for intravenous thrombolysis. However, this system had a lack of interobserver reliability.[24] The *ASPECTS* (Alberta Stroke Program Early CT Score) system was originally developed as a tool to predict the risk of hemorrhagic transformation following IVT but was later adapted to mapping the extent of

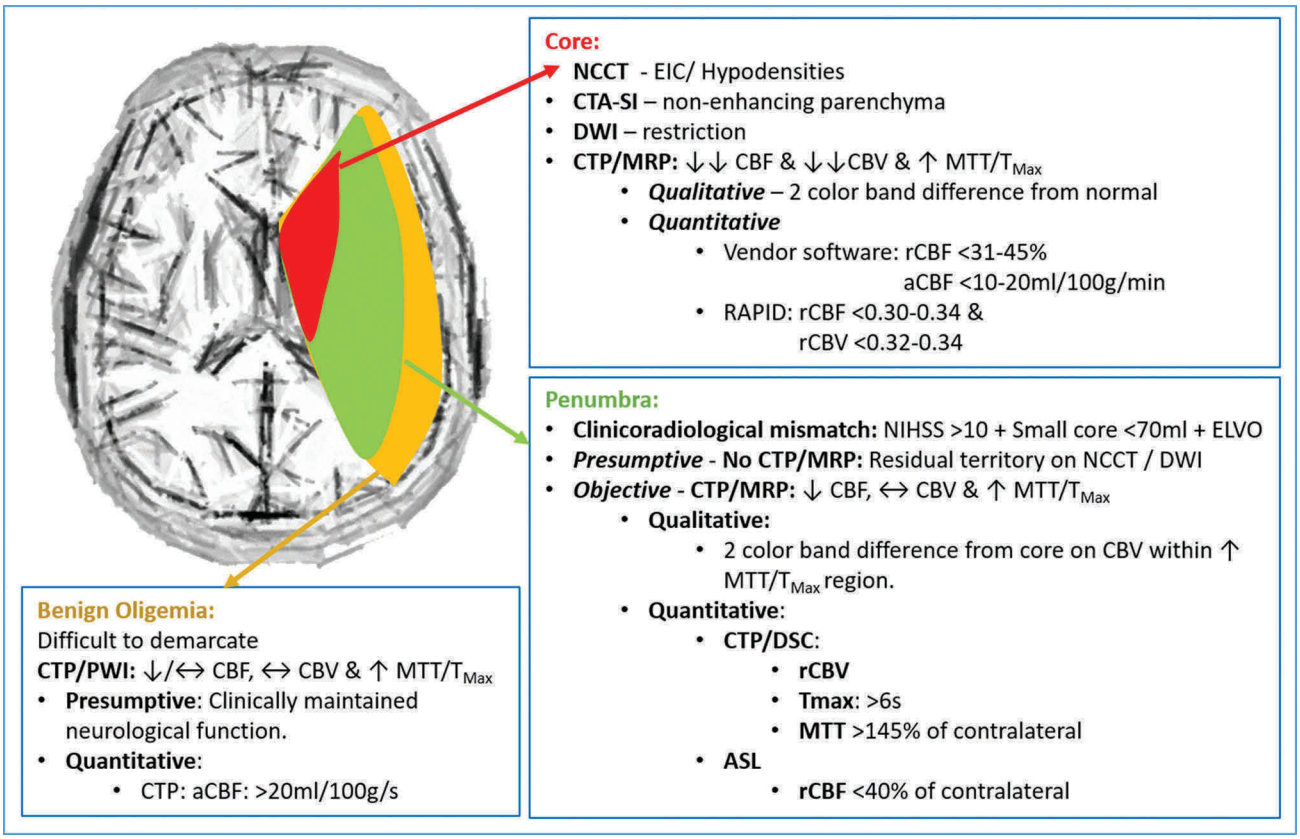

Fig. 1 Zones of ischemia and various imaging indicators. aCBF, absolute CBF; ASL, arterial spin labeling; CBF, cerebral blood flow; CBV, cerebral blood volume; CTA-SI, computed tomographic angiography–source image; CTP, computed tomographic perfusion; DSC, dynamic susceptibility contrast; DWI, diffusion-weighted imaging; ELVO, emergent large vessel occlusion; MRP, magnetic resonance perfusion; MTT, mean transit time; NCCT, noncontrast computed tomography; PWI, perfusion-weighted imaging; T_{Max}, time-to-maximum of the residue function; rCBF, regional CBF; rCBV, regional CBV.

Table 2 Definition of CT signs of ischemia

Sign	Definition
Insular ribbon sign	Loss of the normal insular cortical hyperdensity with EIC
lentiform obscuration sign	Loss of delineation of GWD of the lentiform nucleus
Disappearing basal ganglia sign	Loss of GWD of the basal ganglia
Focal hypoattenuation	Relative hypodensity of regions compared with others
Cortical sulcal effacement and obscuration of the sylvian fissure	Loss of precise delineation of the sulci, accompanied by loss of GWD of the cortical and insular regions secondary to localized mass effect (isolated sulcal effacement is not an EIC because this can occur even in the penumbra)

Abbreviations: CT, computed tomography; GWD, gray–white differentiation; EIC, early ischemic change.

core involvement.[22] The score consists of 10 regions viewed at two levels: ganglionic and supraganglionic (►**Fig. 2**). Involvement of each area results in 1 mark being deducted from the maximum of score of 10. The ASPECTS is therefore a surrogate for core volume, which in itself is a predictor of response to treatment.[25]

The AHA criteria recommend a score of > 6 for thrombolysis or EVT.[6] This does not mean that all patients with a score lower than this are excluded compulsorily. The MR CLEAN required only an LVO and did not depend on the ASPECTS score. Post hoc analysis revealed a good outcome post-EVT in patients with ASPECTS > 4.[26] In our opinion, the ASPECTS must only guide treatment decisions along with careful consideration of the patient's life expectancy, quality of life, and patient/family preferences.

The posterior circulation also has its own 10-point score: the pc-ASPECTS (posterior circulation Acute Stroke Prognosis Early CT Score) that can predict prognosis in basilar artery occlusions (►**Fig. 3**).[27] A score of < 8 results in relatively poor outcomes despite recanalization.[27]

The plain CT can also aid in the detection and localization of LVO by the identification of the dense MCA and MCA dot signs.[23] These are highly specific (95%) but relatively insensitive (52%) for LVO.[28] They indicate a reduced efficacy of IVT.[29]

Magnetic resonance imaging: The stroke MRI protocol should aim to be minimalistic and efficient and should be practiced only in hospitals that have the infrastructure to maintain the door-to-needle or door-to-puncture times within the prescribed limits. Every delay of 30 minutes increases the risk of poor functional outcome by 14%.[30] The basic sequences include DWI, susceptibility-weighted imaging (SWI), fluid-attenuated inversion recovery (FLAIR), and arterial spin labeling (ASL) with a time-of-flight (TOF)

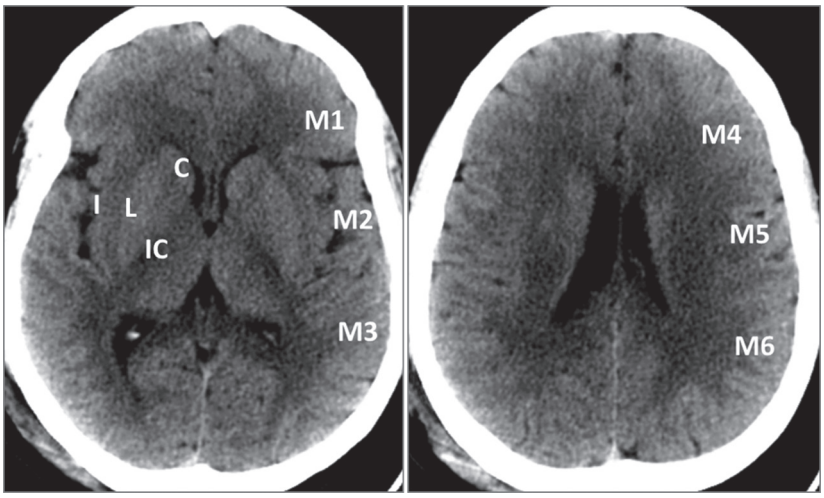

Fig. 2 ASPECTS system. From a maximum of 10, 1 point is deducted for each of area of involvement. The cortical areas are designated M1–3 and M4–6 at the ganglionic and supraganglionic levels, respectively. The insula (I), the deep gray nuclei (C, caudate, L, lentiform nucleus), and the posterior limb of the internal capsule (IC) are the other structures. Also note optimal stroke window settings.

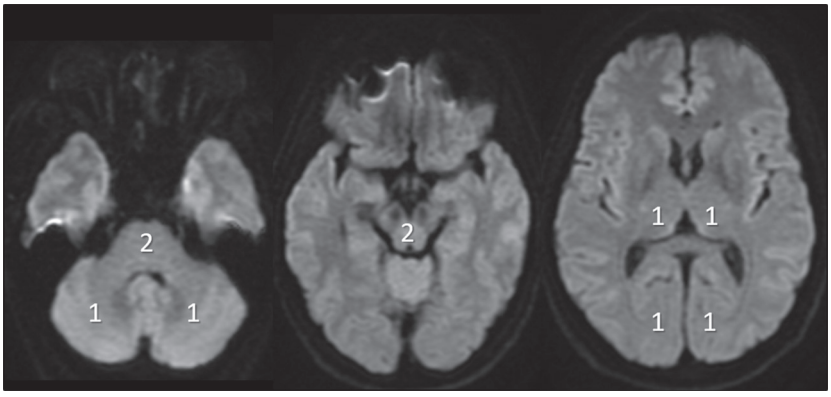

Fig. 3 pcASPECTS system. Each thalamus and occipital region corresponding to the PCA territories is given 1 point each. The midbrain and pons densely populated by gray matter nuclei and white matter tracts are given 2 points each. The cerebellar hemispheres are given 1 point each. Similar to the ASPECTS, points are deducted from a baseline maximum of 10.

angiography of the craniocervical vessels. We examine the utility of each sequence in the management of stroke.

Diffusion-weighted imaging: DWI is the gold standard in hyperacute infarct detection and is more sensitive than CT improving on its sensitivity from < 50% to as much as 88 to 100% with almost equal specificity.[23] Apart from this increased sensitivity, other indications are the presence of ipsilateral extensive chronic ischemic changes, posterior circulation stroke, or wakeup stroke.

Onset of diffusion hyperintensity is within 30 minutes although some animal studies have shown onset even < 10 minutes.[23] This sensitivity can be improved using longer *b* values of 2,000 milliseconds in cases of very early, small, or posterior circulation infarcts.[31] 1.5T is actually superior to 3T due to improved DWI contrast.[32]

In clinical practice, diffusion hyperintensities are generally considered to represent irreversibly infarcted core. However, reversible diffusion hyperintensities (RDH) appear to be a fairly common occurrence seen in a mean of 24% (range: 0–83%) of patients achieving early reperfusion < 3 hours.[33] Reversal appears to be mainly limited to smaller embolic lesions with only a minority achieving complete reversal.[34,35] These reversals also need not necessarily indicate viability because they may be caused by reperfusion induced fluid shifts.[36,37] Their clinical significance is thus highly controversial.[38,39]

Similar to CT, a DWI-ASPECTS can be calculated. Although the AHA criteria do not specify a DWI-ASPECTS cutoff for thrombolysis or MT, studies such as SWIFT-PRIME (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke) have found a score of ≥5 to have good outcomes after successful MT.[40,41]

Volumetric quantification of the infarct core is possible either manually (using an ADC threshold of 600×10^{-6} mm^2/s)[42] or using the automated RAPID (*Ra*pid processing of *P*erfusion and *D*iffusion, iSchemaView) software. Though SWIFT-PRIME[43] and EXTEND-IA (EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy)[44] chose a higher core volume threshold of < 50 and < 70 mL, respectively, for patients presenting within 6 hours, the DAWN trial used a stringent threshold of < 31 and < 21 mL, respectively, for patients younger and older than 80 years presenting in the 6 to 24-hour period.[45]

Similar to FLAIR (discussed below), DWI can also serve as a tissue clock by looking for a b1000-b0 mismatch. This indicates a stroke onset of < 4.5 hours with a sensitivity and specificity of 86% and 89%, respectively, when compared with DWI-FLAIR mismatch.[46]

Fluid-attenuated inversion recovery: The primary utility of FLAIR imaging is to function as an MR "tissue clock" for estimating the time of ictus in unwitnessed or wakeup stroke. At 1.5T, DWI-FLAIR mismatch is the gold standard imaging criterion and reliably indicates < 4.5 hours from ictus.[47] At 3T, this tissue clock is more variable with nearly 44% of patients showing FLAIR changes even < 4.5 hours.[48] The time dependency of FLAIR hyperintensity is also modified by collateral status with patients having good collaterals showing more subtle signal changes than those with poor collaterals.[49] Hence significant interrater variability still remains.[50] Improvements in prediction of time since stroke onset have been achieved using multivariate models that include age, rFLAIR (ratio of signal intensities with a mirror ROI), and perfusion imaging (non-reperfused core T_{max} > 6 seconds).[51] Further, FLAIR can be used to semiquantitatively assess collateral status seen as sulcal hyperintensities.[52]

Susceptibility-weighted imaging: In AIS, severe reduction in cerebral perfusion pressure causes an increase in the ratio of deoxyhemoglobin to oxyhemoglobin by increasing the oxygen extraction fraction (OEF). As a result, increased prominence of draining veins in the hypoperfused region are seen on SWI than in normal brain areas. These are termed "asymmetrically hypointense veins" (AHVs) and have been proposed to be a surrogate marker of the penumbra (►**Fig. 4**).[53] Use of an SWI-DWI mismatch threshold defined as an asymmetry index (ratio of number of venous voxels between hemispheres) of ≥1.75 with a DWI core volume of < 25 mL achieved a higher accuracy in predicting good post-recanalization outcomes than DWI/PWI mismatch (63 vs. 48%).[54] Such calculations, however, require dedicated software, and simpler techniques have failed to show a similar predictive value.

The presence of the vascular susceptibility sign (the surrogate of the dense MCA sign on CT) indicates intraluminal thrombus and can be used as an estimate of clot burden.[55] It can also detect areas of early hemorrhagic transformation and cerebral microbleeds (CMBs) that, when numbering > 10, may be a contraindication for intravenous thrombolysis.[6] However, routine exclusion of CMBs is not recommended.[6]

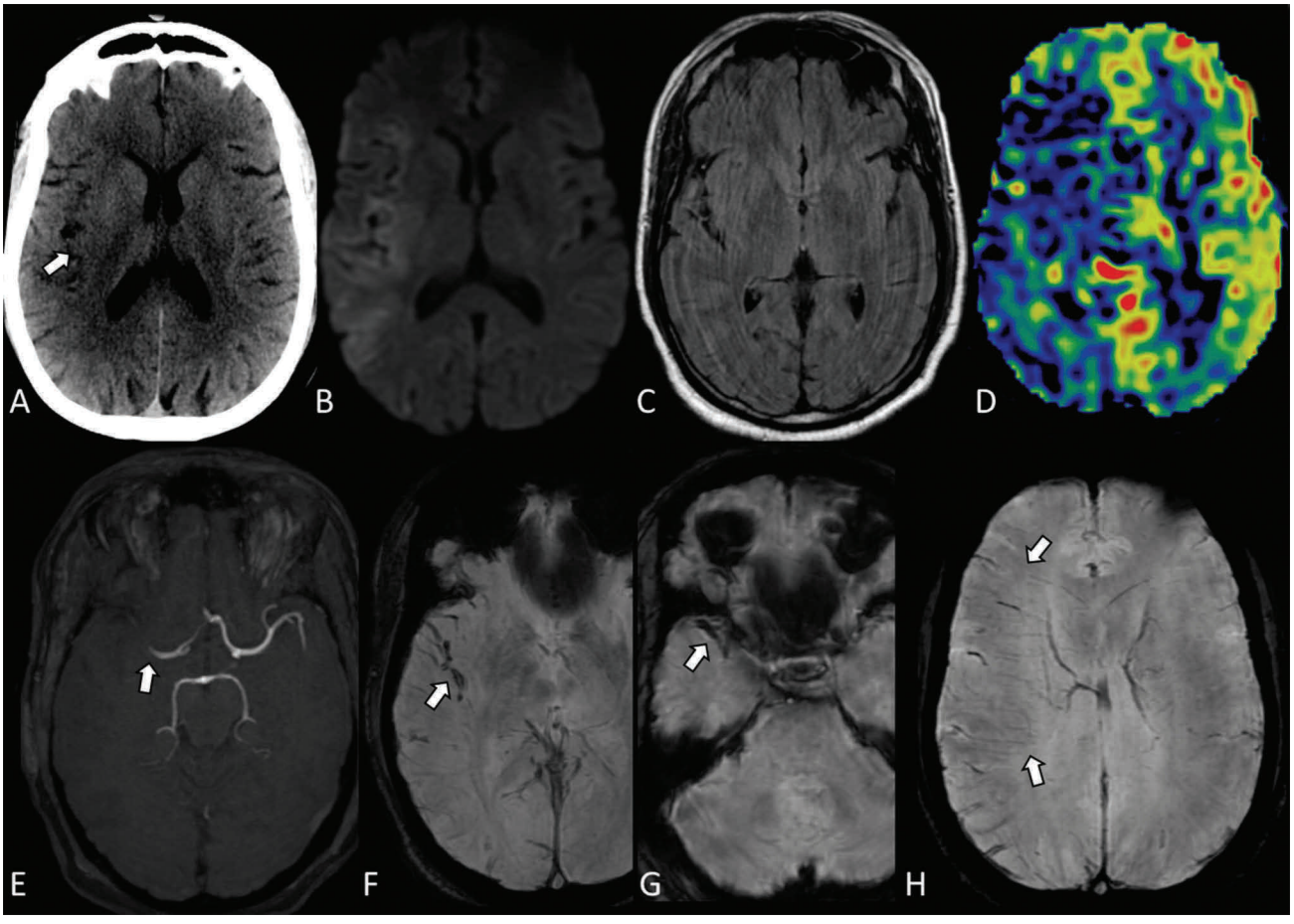

Fig. 4 Multimodal imaging of a representative case: A 49-year-old male present within 4 hours of ictus. **(A)** Plain CT shows subtle loss of basal ganglia gray-white differentiation and insular ribbon sign on the right side (arrow). **(B)** DWI shows diffusion restriction in these areas that are as yet not prominently FLAIR hyperintense **(C)** consistent with onset < 4.5 hours. **(D)** ASL shows areas of hypoperfusion in excess of areas of diffusion restriction consistent with penumbra. **(E)** MRA reveals right MCA occlusion (arrow). **(F,G)** SWI reveals intravascular susceptibility in the M1 and M2 regions (arrows) as well as prominent asymmetrically hypointense veins (AHVs) in the right cerebral hemisphere (**H**, arrows). Note close correlation between SWI-AHV and ASL.

Assessing the Pipes (Vessels): Computed Tomography Angiography and Magnetic Resonance Angiography

Lack of a uniform vessel imaging protocol was cited as one of the reasons for the failure of the negative RCTs published in 2013.[56] Identification of LVO was necessary in all the five landmark trials published in 2015 and has since become standard of care. The presence of LVO predicts limited efficacy of IVT and becomes an indication for EVT.

Computed tomographic angiogram (CTA): The CTA can serve multiple functions: to identify the site of occlusion, allow infarct quantification and perfusion (CTA-SI), predict outcome (clot burden score [CBS]), and allow collateral flow assessment. The speed of CTA is of particular advantage in the evaluation of stroke.

Single-phase CTA: CTA acquisition should be in a caudocranial direction from the aortic arch to the vertex, preferably using bolus triggering. Coverage of the arch and neck vessels allows estimation of the type of arch and navigation difficulty for EVT as well as exclusion of tandem steno-occlusive lesions. Once the site of an occlusion is identified, noting the length of the clot is also useful. Clots longer than 8 mm are resistant to intravenous thrombolysis.[57] It is also useful for estimating the distance that needs to be navigated blindly during stentriever thrombectomy. A CBS assigning 10 points to six vascular segments can also be assigned.[58] Points are reduced for occlusion of each segment (►**Fig. 5**). A lower CBS correlates with lower functional outcomes, larger final infarct volume (FIV), and a higher risk of parenchymal hemorrhage.

The CTA source images (CTA-SI) can be used to analyze the parenchyma itself. In older scanners, CTA-SI was considered CBV weighted, but with faster modern scanners, they have become CBF weighted allowing them to be used as a surrogate for CTP.[59] Lack of parenchymal enhancement on CTA-SI can be used to estimate the core and may predict final infarct better than NCCT ASPECTS.[60,61] CTA-SI can hence be used to confirm NCCT findings. However, a CTA acquired in a relatively early arterial phase (i.e., not allowing for parenchymal enhancement) or with coexistent atrial fibrillation may overestimate core volume by as much as 20%, resulting in unnecessary exclusion of patients.[62]

Finally, CTA can be used for assessing collaterals. Collaterals are of two types: Willisian and leptomeningeal. Willisian collaterals consist of the anterior and posterior communicating arteries. These play an important role in not only maintaining perfusion in occlusion of more proximal vessels such as the internal carotid or basilar artery but also serve as alternative endovascular routes of navigation for EVT. Leptomeningeal collaterals are channels between the distal cortical branches of the pial arteries. They serve as a marker of salvageable penumbra because they maintain perfusion. They also improve clot dissolution by allowing thrombolytic to reach both ends of the occluding thrombus.[63] Multiple schemes exist to grade the degree of collateralization (►**Table 3**). While most of these grading systems, particularly Maas and ASPECTS, reliably predict poor response to therapy, only the Miteff system reliably predicts a good post-treatment functional outcome.[64] This is likely due to its focus on the sylvian region that is the strongest predictor of penumbral mismatch.[65] The modified Tan system is the simplest and has the most interrater reliability. A good collaterals core with a small area of EIC indicates salvageable tissue and may be used to guide reperfusion treatment.

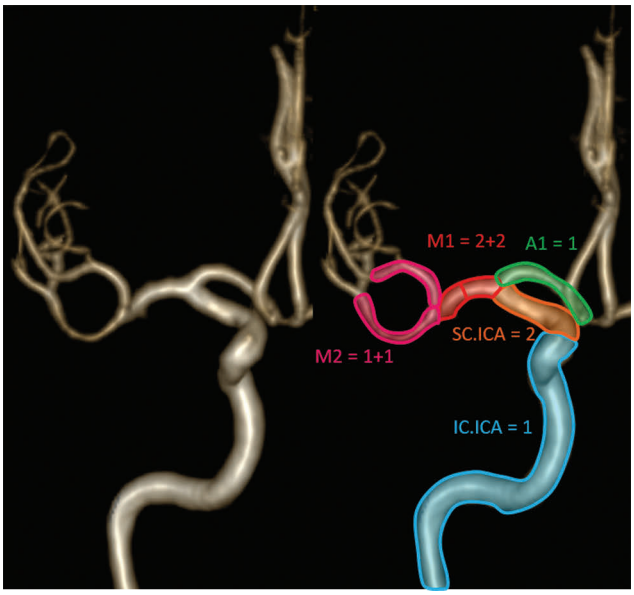

Fig. 5 Clot burden score: The infraclinoid and supraclinoid internal carotid artery (ICA) (IC.ICA and SC.ICA) are assigned 1 and 2 points, respectively. The proximal and distal M1 segments are assigned 2 points each. Each of the M2 segments and the A1 ACA are assigned 1 point each. Occlusion of each segment is deducted from a maximum of 10.

Multiphase CTA: Single-phase CTA suffers from a lack of temporal resolution. Slower retrograde collateral filling may lead to an underestimation of collateral status. This information is provided by multiphase CTA and is an ideal compromise to longer acquisition and processing times of CT perfusion (CTP).[66] The protocol was used in the ESCAPE trial and consists of three phases. Phase 1 covers the arch to vertex in a caudocranial direction and is optimized for the arterial phase by bolus triggering. This phase is similar to single-phase CTA and can be used to grade collaterals similarly. Phases 2 and 3 cover only the cranium (vertex to skull base) and are acquired in as short an interval as possible, resulting in images optimized for the equilibrium/peak venous phase and late venous phases. In patients with known poor cardiac output, an additional phase may be added. The interval between phases is usually approximately 8 seconds (4 seconds for table movement and acquisition each). Pial arterial filling can then be graded using the multiphasic CTA collateral score into six categories that are further trichotomized into three clinically relevant categories of good, intermediate, and poor pial filling. A score of ≤3 is poor and indicates that a patient is unlikely to benefit from recanalization therapy.[66] The results of the PROVE-IT trial comparing multiphase CTA with CTP are awaited.[67]

Assessing Ischemia: Perfusion

There are many disadvantages to using rigid time-based rules for selecting patients for EVT. They cannot be used in wakeup

strokes. They do not take into account the extent of the penumbra that is influenced by other parameters such as collateral status and patient age.[68] Penumbra-based patient selection represents the logical next step in individualized stroke management and may result in better clinical outcomes.[69]

Two methods exist of estimating the penumbra: clinical and radiological.[70] The clinical penumbra is recognized by the presence of a *clinical-radiologic mismatch*, that is, the manifestation of neurologic deficits disproportionate to that expected from the core on imaging. This mismatch is defined as an NIHSS of > 10 in the presence of an ELVO and an imaging core < 70 mL.[70] Radiologic delineation of the penumbra is by means of *perfusion imaging*. Both CTP and MR perfusion (MRP) techniques are available.

The aim of perfusion imaging is to distinguish three regions: the core (irreversibly damaged), the penumbra (needs treatment), and benign oligemia (does not require treatment). These regions are differentiated on the basis of various parameters (►**Table 4**) that are related to each other by the central volume principle: CBF = CBV/MTT.[71]

The common underlying basis of all perfusion techniques is the first-pass principle. Passage of contrast medium into parenchyma causes changes in pixel density or intensity that are proportional to the volume of contrast within. This, in turn, is dependent on regional flow and perfusion.[71] Analysis requires an arterial input function (placed at the A2 anterior cerebral artery) and a venous outflow function (at the superior sagittal sinus). Time density or intensity curves can then be charted for each parenchymal pixel that may then be used to generate parametric maps.

Two techniques of post-processing are possible: conventional and deconvolution methods. Deconvolution methods are superior since they overcome inaccuracies due to variability in cardiac output and allow slower injection rates.[71] They yield time-to-maximum of the residue function (T_{Max}) rather than time-to-peak (TTP).[72]

Few differences exist between CTP and MRP. CTP yields absolute values by virtue of direct proportionality between pixel density and contrast concentrations. MR dynamic susceptibility contrast (DSC) perfusion on the other hand yields relative parameters because signal intensity changes are difficult to convert into absolute concentrations.[73] DSC perfusion has an additional advantage of reducing the total scan time of the stroke MR protocol since acquisition of contrast-enhanced MRA is significantly faster than noncontrast methods.[74] More recently noncontrast techniques such as ASL MR perfusion have also been used in AIS (►**Fig. 4**).[75] Apart from being completely

Table 3 Collateral grading schemes

System	Modality	Grading
Tan	CT angiography	Collateral filling as compared with contralateral hemisphere
		• 0—absent
		• 1—0–≤ 50% filling
		• 2—> 50–99%
		• 3—100% filling
Modified tan	CT angiography	Collateral filling as compared with contralateral hemisphere
		• 0—≤ 50%
		• 1—> 50%
Miteff	CT angiography	Reconstitution of MCA cortical branches
		• 1 (poor)—distal superficial branches only
		• 2 (moderate)—some branches till Sylvian fissure
		• 3 (good)—entire MCA distal to occlusion
Maas	CT angiography	Collateral filling as compared with contralateral hemisphere
		• 1—absent
		• 2—less than
		• 3—equal to
		• 4—greater than
		• 5—exuberant
ASPECTS collateral	CT angiography	Collateral opacification compared with contralateral homologous regions as per ASPECTS system. Maximum total score of 20.
		• 0—not seen
		• 1—less prominent
		• 2—equal or more prominent
Lee	FLAIR MRI	Distal hyperintense vessels on FLAIR
		• 1—absent
		• 2—subtle
		• 3—prominent

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Scores; CT, computed tomography; EIC, early ischemic change; FLAIR, fluid–attenuated inversion recovery; GWD, gray–white differentiation; MCA, middle cerebral artery; MRI, magnetic resonance imaging.

Table 4 Definitions of perfusion parameters

Parameter	Unit	Description
CBV	mL/100 g of tissue	Total volume of blood in a voxel (unit mass of tissue)
CBF	mL/100 g/min	Total volume of blood flowing per minute through unit mass of tissue
MTT	s	Average transit time of blood/contrast through a tissue from arterial to venous side of circulation
TTP	s	Time from start of contrast injection to maximal enhancement
T_{Max}	s	Time from start of contrast injection to maximal residual function in voxel

Abbreviations: CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; T_{Max}, time–to–maximum of the residue function; TTP, time–to–peak.

noninvasive, it allows absolute quantification of CBF.[76] A refinement of the ASL technique with multiple labeling pulses, "multilabel ASL" allows for derivation of arterial transit times (ATTs) that show good correlation with DSC T_{Max} parameters.[77]

Analysis of any perfusion sequence first requires delineation of an area termed the "ischemic tissue at risk" (►**Fig. 1**).[78] This region consists of the core, penumbra, and oligemic tissue, although the latter is technically not at risk of recruitment into the core. Virtually all patients with an ELVO will show a prolongation of time-based perfusion parameters due to circuitous collateral circulation.[70] An MTT > 145% or T_{max} prolonged > 6 seconds can be used to delineate the tissue at risk.[44,79]

The next step is to demarcate the *core*. The core is defined on perfusion primarily by severe reductions in both CBF and CBV.[80,81] To counter the higher variability of absolute values, relative values normalized to contralateral normal hemisphere are more universally used to define the core. rCBF thresholds of < 31 to 45% compared with unaffected brain have been used to define the core.[44,79,81]

Once the core has been demarcated, the *penumbra* is represented by the residual area within the ischemic area at risk defined by time-based parameters. Objectively, the penumbra is characterized by moderate reductions in CBF but maintained or near-normal CBV within the area of prolonged T_{max}/MTT.[80] With ASL, an rCBF threshold of 40% (vs. contralateral hemisphere) was found to best define the penumbra.[82]

Oligemic tissue is the most difficult to differentiate radiologically but may be somewhat defined by regions having near-normal CBF but prolonged MTT/T_{max}.[80] Oligemia may also be clinically deduced by evidence of intact neurological function from within the affected territory.

Though these basic principles are relatively well established, the method of determination and optimum cutoffs for defining each parameter remain controversial and nonstandardized.[79] This is due to this inherent inter- and intravendor (between various software versions) variability that has prevented more universal utilization of perfusion protocols in AIS.[79,83] To counter this variability, an automated standardized software, termed "RAPID" was developed that can be used for both CT and DSC perfusion. This software offers generalizability as well as accuracy with lowest rates of overestimation of the FIV and malignant mismatch profile.[84,85] The data are analyzed online with results being available within 5 to 7 minutes. It has been validated in multiple RCTs such as DAWN, DEFUSE, EXTEND-IA, and SWIFT-PRIME.[43,45,86,87] Using this software, rCBF and rCBV thresholds of 0.30–0.34 and 0.32–0.34, respectively, most accurately predicted FIV in patients who achieved complete reperfusion.[88] Absolute value thresholds of aCBF 27.8 mL/100 g/min, aCBV 2.1 mL/100 g, and aMTT 7.3 seconds allow accurate differentiation of core and penumbra.[80]

Although many controversies exist regarding the optimal method of qualitative analysis, a simple method is to utilize a 6-point rainbow scale with a difference of at least two color bands used to define the tissue at risk (on CBF and MTT/T_{max} maps) and core (on the CBF and CBV maps).[89,90]

Perfusion imaging has an important role in selecting patients presenting < 6 hours with an ASPECTS < 6.[6] If the penumbra involves eloquent areas, EVT may be considered if the patient or family is apprised of the higher risk of complications. In those presenting in the 6 to 24 hours period, perfusion imaging can aid in patient selection by the demonstrating the robustness of perfusion in the residual territory (i.e., differentiation penumbra versus oligemia and extent of penumbra). Similarly, it may be used to select patients with wakeup stroke with an unknown time of onset.

Assessing Penumbra: Core/Ischemia Mismatch

Once these areas have delineated, calculation of a core/penumbra mismatch aids in gauging the expected outcomes of EVT. Volumes may be calculated manually using the ABC/2 calculation (A, B, and C are axial and craniocaudal dimensions respectively) with acceptable accuracy.[91] Patients can then be categorized into four basic profiles: malignant, small core, target-mismatch, and no mismatch (►**Fig. 6**).[92] A *malignant* profile is defined by a core volume of > 100 mL. *Small core* by definition does not qualify as mismatch as this requires a ≥10 mL difference between DWI and PWI.

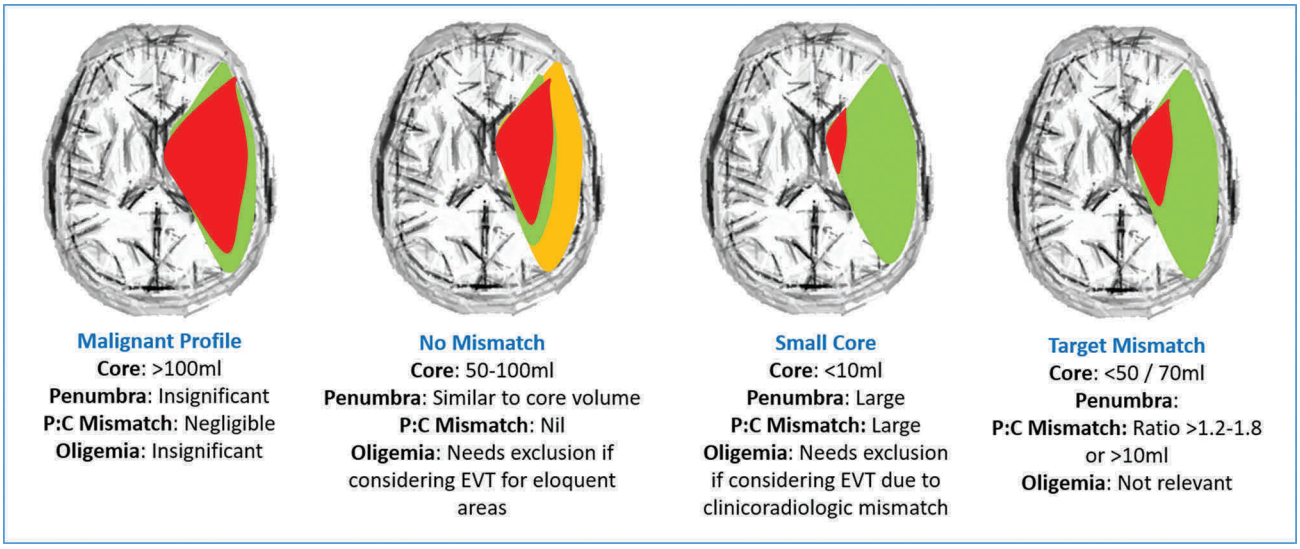

Fig. 6 **Core/penumbra mismatch, four basic profiles**: malignant, small core, target-mismatch, and no mismatch.

Target mismatch includes patients who have a penumbra-to-core ratio of at least 1.2 (EXTEND-IA) or 1.8 (SWIFT-PRIME and DEFUSE 3) and a core size of < 70 mL or < 50 mL (in EXTEND-IA and SWIFT-PRIME, respectively).[43,44] A difference of > 10 mL was also required in the SWIFT-PRIME trial. *No mismatch* profiles are those that do not fit into any of the other categories. Rates of hemorrhagic transformation are high in those with a malignant profile, and revascularization is harmful in such patients. Reperfusion may be futile in those with a well-compensated small core or no mismatch that do not have significant penumbra. The ideal patient is therefore the one with the target mismatch in whom clinical outcomes most improve after revascularization. Perfusion-based selection of patients for EVT is far from standardized and has many drawbacks. Technology and protocols for processing are yet to reach maturity and are an ongoing focus of research.

Table 5 CT protocol and imaging assessment

Sequence	Utility
NCCT	• Core
	◦ ASPECTS
	◦ Volume
	◦ Eloquent area involvement
	◦ Subjective tissue clock—degree of hypodensity (EIC/evolving/established)
	• Hemorrhage
	◦ Exclude primary ICH
	◦ Hemorrhagic transformation
	• Occlusion
	◦ Site of occlusion—hyperdense artery sign
	• Prognosticators
	◦ Leukoaraiosis
	• Chronic infarcts
	◦ Hints at etiology
	◦ If in same region—consider DWI
CTA–SI	• Core—confirmatory
CTA (triple phase > single phase)	• Occlusion
	◦ Site of occlusion
	◦ Length of thrombus
	• Collateral status (shows retrograde filling also)
	◦ Scoring
	◦ Delay, degree of filling—triple–phase CTA
	• Proximal including neck vessels
	◦ Tandem lesions/stenoses
	◦ Arch morphology, access vessels
CTP	• Mismatch profile
	• Penumbra vs. oligemia
	• Permeability—risk of hemorrhagic transformation

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Scores; CTA, computed tomographic angiography; CTA–SI, CTA–source image; CTP, computed tomographic perfusion; DWI, diffusion–weighted imaging; EIC, early ischemic change; ICH, intracerebral hemorrhage; NCCT, noncontrast computed tomography.

Conclusion

The treatment of AIS with LVO has been revolutionized by the introduction of endovascular thrombectomy. Improving outcomes requires a streamlined workflow from diagnosis, clinical assessment, imaging, and triage to treatment. The radiologist must choose a set protocol for each time phase of presentation of AIS and have a systematic image analysis paradigm (Tables 5, 6, ►**Fig. 7**). The aim of imaging is to rapidly

Table 6 MRI protocol and imaging assessment

Sequence	Utility
DWI	• Core
	◦ ASPECTS
	◦ Volume
	◦ Eloquent area involvement
SWI	• Occlusion
	◦ Site of occlusion
	◦ Length of thrombus
	• Hemorrhage
	◦ Exclude primary ICH
	◦ Hemorrhagic transformation
	• Penumbra
	◦ DWI–SWI mismatch
FLAIR	• Tissue MRI clock
	◦ Not hyperintense = 4.5 h
	• Collateral status—ivy sign (qualitative)
	• Leukoaraiosis—prognosticator
	• Chronic infarcts?
	◦ Hints at possible etiology
MRA TOF/CEMRA	• Site of occlusion
	◦ Only antegrade direction of flow—does not show collaterals (length of thrombus only on SWI)
	• Proximal including neck vessels
	◦ Tandem lesions/stenoses
	◦ Arch morphology, access vessels
PWI (ASL/DSC)	• Mismatch
	• Penumbra vs. oligemia

Abbreviations: ASL, arterial spin labeling; ASPECTS, Alberta Stroke Program Early Computed Tomography Scores; CEMRA, contrast–enhanced MRA; DSC, dynamic susceptibility contrast; FLAIR, fluid–attenuated inversion recovery; DWI, diffusion–weighted imaging; ICH, intracerebral hemorrhage; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PWI, perfusion weighted imaging; SWI, susceptibility–weighted imaging; TOF, time of flight.

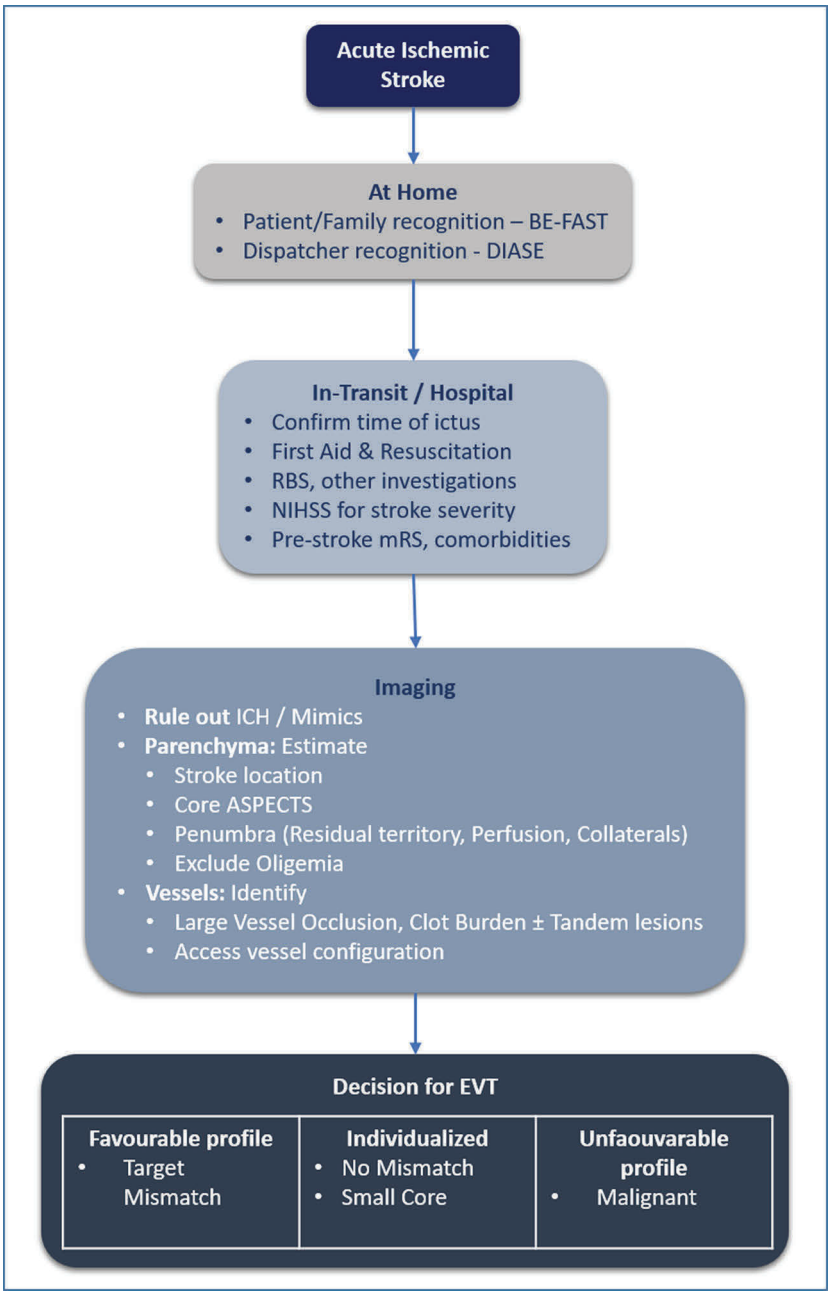

Fig. 7 A set protocol for each time phase of presentation of AIS and a systematic image analysis paradigm.

identify patients with an LVO and a significant salvageable penumbra. Patient selection and endovascular management are further discussed in part 2 of this review.

Conflict of Interest
None.

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