BJR, 2024, **97**, 1078–1087
https://doi.org/10.1093/bjr/tqae050
Advance access publication: 15 March 2024
Review

Imaging in acute ischaemic stroke: assessing findings in light of evolving therapies

Patrick Frias, MD[1], Rajkamal S. Khangura, MD[2], Bahram Varjavand, MD, PhD[2], Matthew D. Alexander , MD, MS[1,2,*]

[1]Departments of Radiology and Imaging Sciences, University of Utah, Salt Lake City, UT 84132, United States
[2]Neurointerventional Radiology, Sutter Sacramento Medical Center, Sacramento, CA 95816, United States

*Corresponding author: Matthew D. Alexander, MD, MS, Neurointerventional Radiology, Sutter Sacramento Medical Center, 3161 L Street, Sacramento, CA 95816, United States (Matthew.alexander@sutterhealth.org)

Abstract

Acute ischaemic stroke (AIS) is a debilitating disease for which effective therapies are now available. Effective identification of candidates for therapy relies heavily on noninvasive imaging that must be interpreted accurately in a short timeframe. This review summarizes the evolution of AIS therapies and the implications for noninvasive imaging. The review concludes with consideration of longstanding assumptions about imaging of ischaemic stroke and potential paradigm shifts on the horizon.

Keywords: acute ischaemic stroke; thrombolysis; mechanical thrombectomy; advanced imaging.

Introduction to ischaemic stroke

Stroke is a leading cause of death and long-term disability. In the United States alone, about 795 000 people have a stroke annually; approximately one in four of these is a recurrent stroke.[1] Between 2018 and 2019, the estimated combined direct and indirect cost of stroke in the United States was $56.5 billion; direct medical costs related to stroke are projected to more than double by 2035.[1] Stroke is a generic term for an acute onset of neurologic symptoms.[2] The majority of strokes are ischaemic in most geographic locations, while haemorrhagic strokes predominate in East Asia.[1] Subtypes of ischaemic stroke include cardioembolic, atherosclerotic, and small vessel disease causing lacunar infarcts.[1,2] Less common aetiologies exist, and cryptogenic strokes of no clear source account for a substantial proportion of stroke cases.[2] Additionally, many stroke patients have many vascular risk factors and potential sources of stroke such that identifying the clear cause is difficult.

The pathophysiology of acute ischaemic stroke (AIS) involves acute arterial occlusion that causes inadequate perfusion and initiates an ischaemic cascade that affects brain parenchyma. This cascade leads to permanent cell death in a variable proportion of tissue downstream to the occlusion.[2,3] Multiple imaging techniques can demonstrate changes in the brain caused by AIS. As such, imaging criteria have been incorporated into AIS workflows to determine which patients may benefit from available treatments. Improper selection of patients for therapies—thrombolysis or mechanical thrombectomy (MT)—can lead to increased rates of complication including intracranial haemorrhage and herniation. The general concept guiding the evaluation of candidacy for these therapies is the identification of a large vessel occlusion (LVO) and salvageable tissue that remains viable but is at risk of infarction without intervention. A brief review of the history of AIS treatment illustrates how such candidacy considerations have changed over time and the role of noninvasive imaging in evaluating patients. This can then be followed with a reconsideration of imaging features of AIS and modifications that might be warranted in the era of effective AIS therapies.

History and future of AIS treatment

Treatment of AIS has evolved at a rapid pace over the past several decades. Intravenous thrombolytic therapy with tissue plasminogen activator (tPA) was established as an effective treatment for AIS with the 1995 NINDS study, which demonstrated that patients treated with IV tPA within 3 h of symptom onset had improved clinical outcomes.[4] Subsequent results supported the extension of IV tPA candidacy up to 4.5 h since a patient was last known well (LKW) and in extended windows for certain patients.[5,6]

Endovascular approaches to clot disruption or removal were described for decades, but multiple randomized controlled trials did not demonstrate efficacy until 2015 with the publication of the MR CLEAN trial.[7] This was followed quickly by positive results for MT in the ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA trials and subsequent patient-level meta-analysis of these trials in the HERMES cohort.[8-12] By 2016, a new paradigm existed for the treatment of AIS. At this time, high-level evidence supported mechanical thrombectomy to treat large vessel occlusions in the anterior circulation within 6 h since LKW and with salvageable tissue downstream to the LVO as indicated by an Alberta Stroke Program Early CT Score (ASPECTS) of 6-10.[13] The positive MT trial results beginning in the

Received: 6 October 2023; **Revised:** 21 February 2024; **Accepted:** 22 February 2024

mid-2010s coincided with advances in endovascular devices and techniques specific to this procedure, and these trials also confirmed the role of noninvasive imaging in the assessment of candidacy.

Building on the success of trials in the HERMES cohort, potential expansion of inclusion criteria was sought. Patients with AIS more than 6 h since LKW were enrolled in the DAWN and DEFUSE 3 trials.[14,15] While inclusion criteria differed somewhat between these two trials, their results demonstrated the efficacy of MT up to 24 h in patients with salvageable tissue. Notably, these were the first trials with positive results for MT that utilized perfusion imaging in their inclusion criteria. The 2021 AURORA study analysed patient-level data from extended window trials.[8,9,14-18] This pooled analysis confirmed a reduction in disability at 90 days in patients undergoing MT with candidacy based on imaging mismatch or clinical mismatch to identify salvageable tissue.[16]

Up to this point, all positive results were in trials studying patients with an anterior circulation LVO. Basilar artery occlusions impart substantial morbidity and mortality, so many providers elected to offer MT in these circumstances up to 24 h since LKW in the absence of randomized controlled trial data to support the practice. Indeed, unwillingness to enrol patients in trials due to the potential ethical implications in this cohort delayed the completion of trials examining these questions. When results of BEST and BASICS trials failed to show significant benefits of MT, many centres did not substantially alter their treatment approaches for posterior circulation LVO.[19,20] In 2022, the BAOCHE and ATTENTION trials confirmed the benefit of MT in patients with basilar occlusion.[21,22] These trials relied on noninvasive imaging for inclusion criteria, either the posterior circulation ASPECTS or pons-midbrain index.[21-23]

Acute ischaemic stroke treatment candidacy long followed the paired assumptions that sufficient salvageable tissue must be identified, and large core infarct excludes patients from therapy due to the high risk of poor outcomes, often mediated by haemorrhagic conversion or herniation. These assumptions are now being challenged by large core infarct treatment trials. The first of these was RESCUE-JAPAN LIMIT, which was published in 2022.[24] While demonstrating the benefit of MT in patients with ASPECTS of 3-5, its publication did not lead to widespread changes in MT practices due to concerns for applicability beyond the unique features of stroke care delivery in Japan.[24] Specifically, a high number of patients analysed with MRI in the acute interval was hard to extrapolate to systems in other countries with predominantly CT-based workflows. Additionally, the standard dose of IV tPA in Japan differs from doses elsewhere and was a potential confounder. Subsequent trials helped clarify the benefit of MT for patients with large core infarcts. SELECT2 and ANGEL-ASPECTS both demonstrated improved functional outcomes at 90 days for patients with ASPECTS 3-5 with anterior circulation occlusions treated with MT within 24 h since LKW.[25,26] Surprisingly, a benefit was identified across multiple subgroups, including patients with very large core infarcts or no identified salvageable tissue as defined by perfusion imaging results. The benefit of MT in the setting of large core was confirmed with results of the TENSION trial.[27] While noninvasive imaging remains crucial for the assessment of AIS patients, previous assumptions about imaging of core infarcts are now being challenged. Results of the TESLA trial were released in 2023, showing no significant benefit for MT in patients with a more inclusive ASPECTS range of 2-5, although results approached significance with a benefit trend mirroring the previous large core trials.[28] At the time of publication, additional large core AIS trial has completed enrollment, but results are pending—LASTE; meta-analysis of currently published results confirms benefit of MT in patients with large infarct.[29-31]

Building on the strength of previous AIS trials and advances in devices and techniques to safely reach occlusions, attention now turns to distal locations in smaller vessels. Such medium vessel occlusions (MEVOs) and distal vessel occlusions (DEVOs) are the subject of the ESCAPE MEVO, DUSK, and DISTAL trials.[32-34] Noninvasive imaging will remain vital in the evaluation of patients with such pathology. To best equip diagnostic radiologists to interpret AIS imaging studies, we will summarize noninvasive modalities and protocols considering the above-described progression of AIS treatment. CT-based evaluation predominates at most stroke centres. As such, CT techniques will be reviewed first. This will be followed by special consideration for MRI findings in AIS.

Noninvasive imaging in AIS

Non-contrast CT (NCCT) is the first-line study for AIS evaluation at most sites. NCCT became integral in AIS management with the adoption of IV tPA therapy and remains the best option for excluding intracranial haemorrhage, which is a contraindication for both thrombolysis and MT. Additionally, NCCT has been thought to indicate the size of early ischemic change. Initial IV tPA inclusion criteria required early ischemic change on CT to be less than one-third of the MCA territory.[4] This was subsequently quantified with ASPECTS.[13] Ranging from 0-10, a point is deducted for hypodensity or loss of grey matter-white matter differentiation in ten total sites: caudate, putamen, internal capsule, insular cortex, anterior MCA territory, MCA territory lateral to the insular cortex, posterior MCA territory, supra-ganglionic anterior MCA territory, supra-ganglionic lateral MCA territory, and supra-ganglionic posterior MCA territory (Figure 1). Notably, scoring is performed on a single image at the level of the basal ganglia and a single image at the level of the lateral ventricles immediately above the basal ganglia.[13] As described above, initial studies confirmed the benefit of MT for patients with ASPECTS 6-10. However, recent trials suggest benefit exists for patients with ASPECTS 3-10 within 24 h since LKW.[29-31]

With the success of ASPECTS for anterior circulation LVO, a similar approach was adopted for the posterior circulation and included in the inclusion criteria for basilar occlusion MT trials. The 10 points for pc-ASPECTS are derived from six anatomic locations: pons, midbrain, thalamus, cerebellar hemisphere, and occipital lobes.[35] Owing to the high morbidity inherent in infarcts in these locations, two points each are subtracted for any early ischaemic change involvement in the pons and midbrain regardless of size or laterality.[35] Single points are subtracted for each thalamus, occipital lobe, and cerebellar hemisphere[35] (Figure 2). Notably, while pc-ASPECTS is commonly evaluated with NCCT, CT angiography (CTA) source images demonstrate higher sensitivity.[35] Inclusion criteria for BAOCHE required pc-ASPECTS 6-10 for enrolment, while ATTENTION

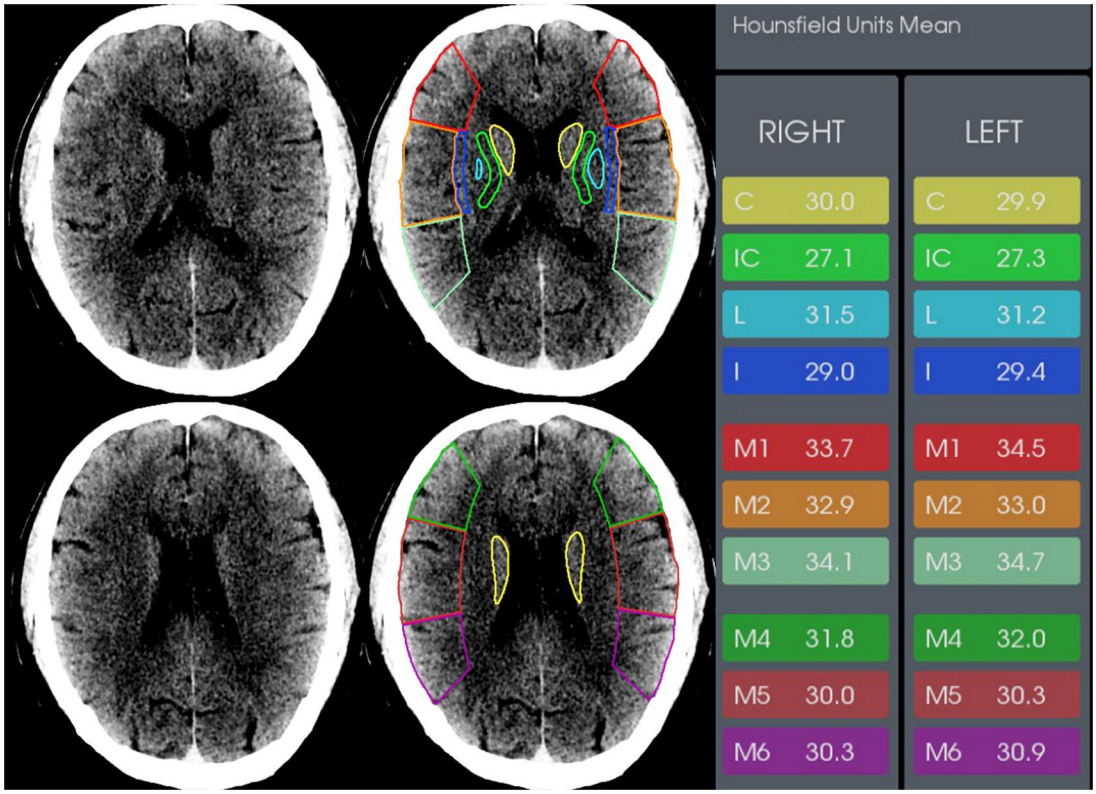

Figure 1. Axial NCCT images through the basal ganglia and supraganglionic level for ASPECTS analysis. Images are adapted from automated output of ASPECTS scores generated by RapidAI (iSchemaView, Golden, CO). Ten middle cerebral artery territory regions are noted. Abbreviations: C = caudate, IC = internal capsule, L = lentiform nuclei, I = insula. Caudate is visualized on both levels).

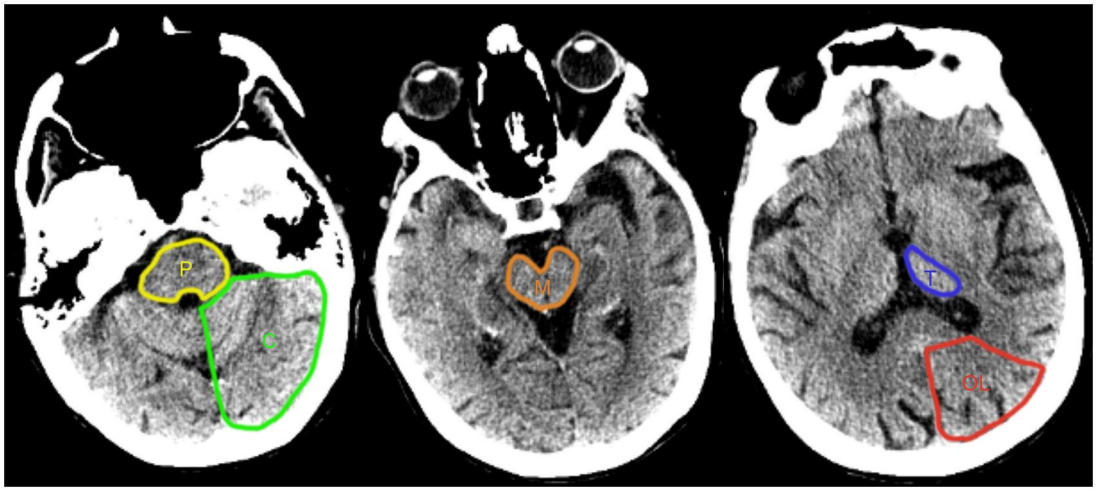

Figure 2. Axial NCCT images demonstrating regions for pc-ASPECTS scoring. Abbreviations: P = pons, C = cerebellum, M = midbrain, T = thalamus, OL = occipital lobe.

required a score of 6-10 for patients younger than 80 years old or 8-10 for patients older than 80.[21,22]

An alternative method for assessing posterior circulation strokes is the pons midbrain index (PMI).[23] This scale ranges from 0 for normal to a worst score of 8. The pons and midbrain are evaluated on either side.[23] A 0 is assigned for normal appearance, 1 for <50% hypoattenuation, and 2 for >50% hypoattenuation[23] (Figure 3). PMI was also used for BAOCHE and ATTENTION inclusion criteria, with a score less than 3 required for enrolment.[21,22] In addition to NCCT, CTA is a mainstay of AIS evaluation at most institutions. CTA identifies the sine qua non of AIS cases that can be intervened upon—the occluded vessel. The importance of this function is emphasized by the focus by commercial vendors to identify occlusions with artificial intelligence (Figure 4A). However, CTA offers much more than the presence of a clot. CTA of the head and neck offers valuable information to the interventionalist, including the location and length of the clot, the presence of tandem thrombus or steno-occlusive disease, and anatomic considerations like arch morphology or

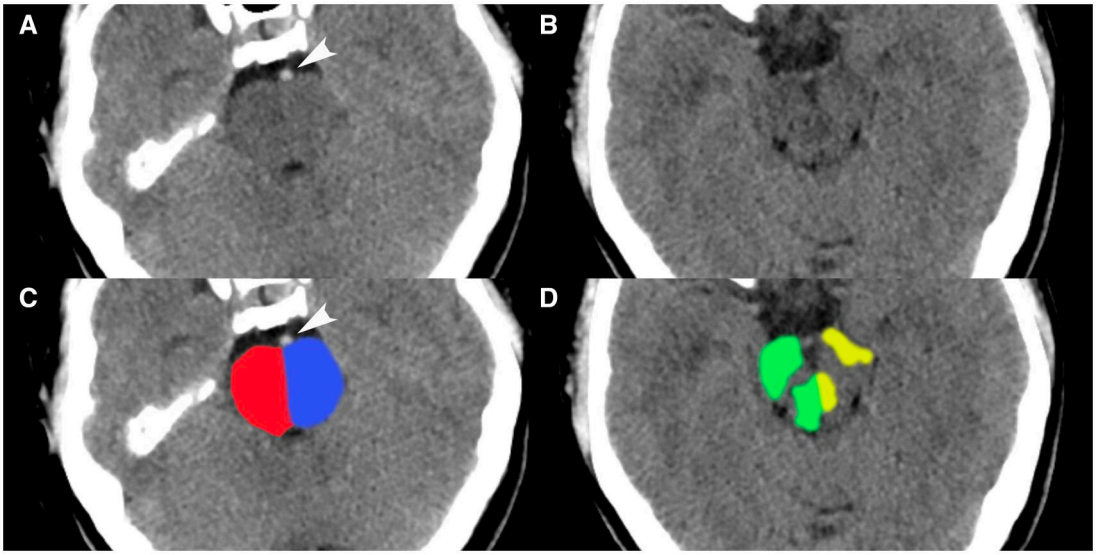

Figure 3. Axial NCCT images through the (A) pons and (B) midbrain in a patient with altered mental status. Note the hyperdense basilar artery due to occlusion (arrowhead). Annotated images demonstrate PMI score for these levels through the (C) pons and (D) midbrain. The right pons (red), left pons (blue), and right midbrain (green) each score two points for infarct involving >50% of these areas. The left midbrain (yellow) demonstrates infarct occupying <50% of the area and receives a score of 1. Total PMI of 7 indicates the patient is not a candidate for MT. >50% hypoattenuation.

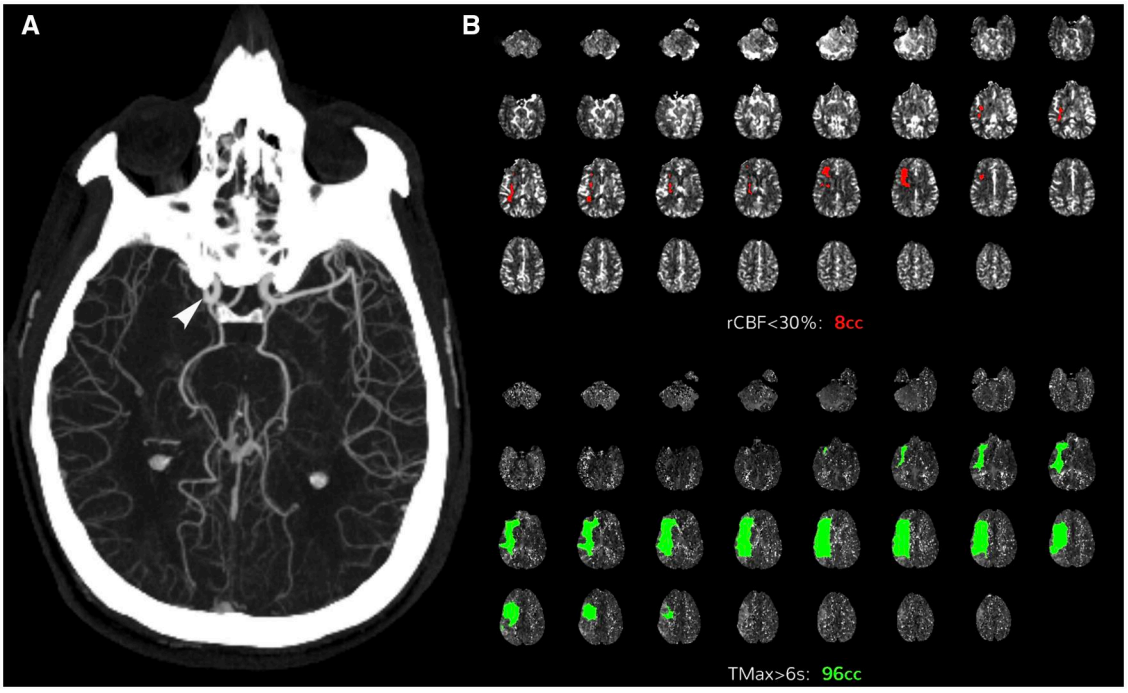

Figure 4. (A) Axial maximum intensity projection image (MIP) from a patient with acute onset of right MCA syndrome demonstrates LVO of the right middle cerebral artery (arrowhead). (B) CTP output demonstrates rCBF and TMax images. Both images are automated outputs from the Viz.ai application (Viz.ai, San Francisco, CA).

dolichoectasia that can affect equipment selected for the MT procedure. Multiphase CTA can help assess collateral status in addition to the occlusion identification provided by single pass CTA. Multiple collateral scoring systems have been proposed and validated.[36] Collaterals have been shown to predict outcomes in AIS patients, but scoring systems have not been incorporated into the designs of most AIS trials to date.[37] One notable exception is the MR CLEAN-LATE trial, which utilized CTA collateral score in patients presenting 6-24 h since last known well. Interpretation of the positive results of this trial suggests MT candidacy could potentially be determined based on presence of adequate collateral flow alone.[38]

CT perfusion (CTP) is a useful tool in the workup of AIS whose role has changed through the course of AIS trials. By analysing the temporal changes in enhancement in a slab of the brain on multiple sequential acquisitions, perfusion of the tissue can be assessed by measuring tissue density as contrast perfuses parenchyma. A variety of processing suites exist to provide mean transit time (MTT) or time to peak (TTP or

TMax), cerebral blood volume (CBV), and cerebral blood flow (CBF). MTT/TTP/TMax demonstrates the duration required to perfuse a specific region of the brain; parenchyma downstream to an arterial occlusion will have a prolongation of these times.[39] CBV represents the quantity of blood in a specific volume of brain parenchyma and is calculated as the area under the concentration-time curve.[39] CBF represents the amount of blood that flows through a specific quantity of brain tissue in a specific amount of time and is calculated by dividing CBV by MTT/TTP/TMax.[39] Heuristically, prolonged transit can be thought of as representing all tissue at risk due to an occlusion, whereas CBF under a certain threshold has been shown to correspond to infarct and has been considered representative of core infarct in the acute setting[39] (Figure 4B). The volume of salvageable tissue, known as the penumbra, is calculated by subtracting the core volume from the volume of tissue at risk.[39] While software exists to provide calculated volumes based on perfusion data, it is important to remember that perfusion imaging is affected by a patient's underlying physiology. Scenarios in which conditions differ from the typical AIS patients with solitary occlusions were analysed in the work validating perfusion imaging. This explains the well-known limitations of perfusion imaging in the setting of low cardiac output, tandem stenosis, arrhythmia, chronic occlusion, or robust perfusion via collaterals[40] (Figure 5). Additionally, a proper selection of arterial and venous regions of interest is needed for proper evaluation.[40] Furthermore, it must be emphasized that perfusion imaging has only been validated in the anterior circulation. The PRECISE trial seeks to validate the role of perfusion imaging in the setting of posterior circulation AIS and is currently enrolling. As with collateral scores, the hypoperfusion intensity ratio (HIR) based on CTP holds some predictive value but has not yet been incorporated into current treatment algorithms.[41-43]

Initial trials utilizing perfusion imaging for patient selection did not demonstrate the efficacy of MT. However, perfusion imaging was a mainstay of the extended window trials and is now included in the workflow of many centres.[14-16] With the benefit of MT in patients with large core infarcts, the utility of perfusion imaging has been debated. While its role may diminish if quantification of penumbra is less impactful on decision-making, it can still aid in the detection of occlusions that are difficult to identify on CTA, particular occlusions of smaller, more distal arterial branches. This is a common occurrence in studies with motion degradation or poor bolus timing. A perfusion deficit can easily prompt further scrutiny of a CTA initially deemed normal. This is

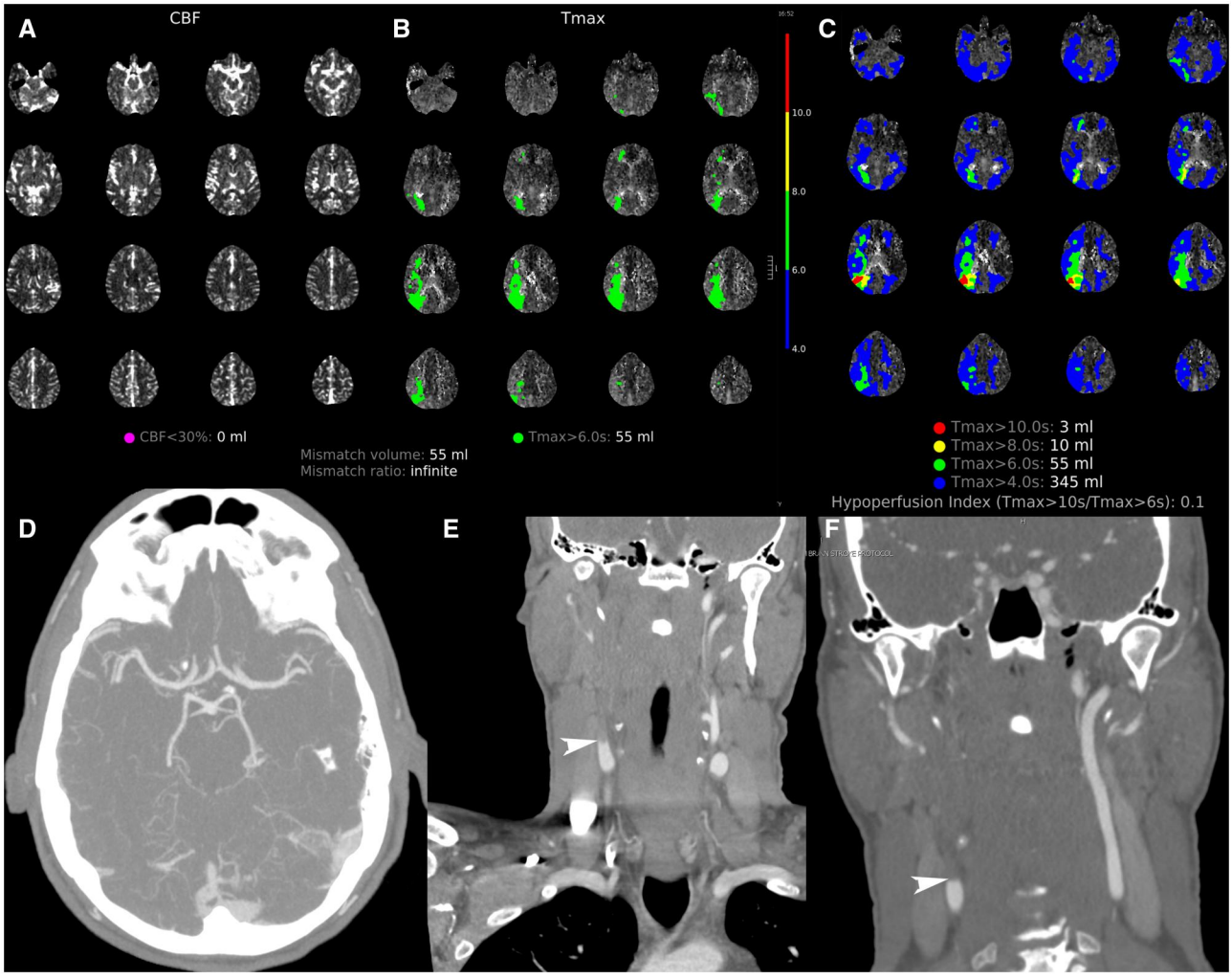

Figure 5. Output of CTP processing demonstrating (A) CBF and (B) TMax >6 s. (C) demonstrates TMax findings with different thresholds. (D) Axial MIPS of CTA images demonstrate no intracranial LVO. (E) and (F) show occlusion (arrowhead) of the cervical right internal carotid artery with widely patent left.

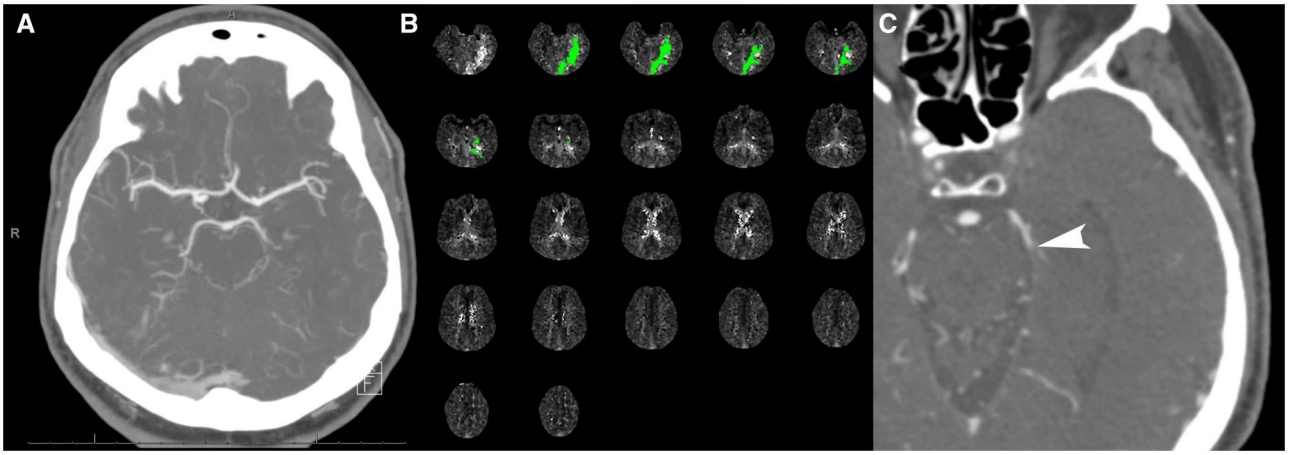

Figure 6. An elderly man presented to an outside hospital with a left middle cerebral artery syndrome. NCCT was normal, and the facility did not have the capability to perform CTA. IV tPA was administered, and the patient was transferred. Symptoms largely improved during transit. (A) CTA demonstrated no LVO. (B) TMax images from post-processed CTP showed delayed transit to the left posterior cerebral artery territory. (C) Further evaluation of the CTA identified occlusion of a P2 branch (arrowhead) of the left posterior cerebral artery.

particularly true in the era of Tenecteplase (TNK), a new intravenous thrombolytic that is replacing tPA at many centres. TNK has higher rates of lysis, but this can result in incomplete lysis that ends with smaller clots in more distal locations. Early anecdotal experiences with TNK indicate common occurrences in which thrombolysis is administered at one location and then partial lysis occurs during transfer to a location that can offer MT services. CTP can help identify locations of such occlusions by demonstrating regions of perfusion deficits (Figure 6).

Functions achieved with CT have effective analogues with MRI. Diffusion-weighted imaging (DWI) has long been interpreted to identify infarct. DWI can identify ischaemic changes in the brain within 3 min of insult.[44] However, effective AIS therapy has led to the identification of DWI reversibility. In some patients with successful recanalization, a lower volume of tissue with DWI hyperintensity is noted on repeat MRI.[45] However, durability of this reversal is a contentious issue, and further analysis of the phenomenon is needed.[46,47] Fluid attenuated inversion recovery (FLAIR) hyperintensity in areas affected by infarct becomes visible within a matter of hours.[44] Comparing DWI and FLAIR presents an opportunity for evaluation unique to MRI. DWI-FLAIR mismatch, ie DWI hyperintensity without corresponding FLAIR hyperintensity, has been shown to identify patients with stroke symptom onset within 4.5 h with high specificity[44] (Figure 7). This imaging finding can be used as a surrogate for the time of symptom onset when such timing is unknown. This is particularly beneficial in the setting of wake-up stroke symptoms. In addition to non-contrast MRI applications, MR angiography and MR perfusion can also be used much like to CTA and CTP for the evaluation of patients with AIS.

An additional potential advantage of MRI is in elucidating prognosis after AIS treatment. The Pons-Midbrain and Thalamus score (PMT) has been shown to correlate with clinical outcomes following mechanical thrombectomy, outperforming pc-ASPECTS with respect to the prediction of post-treatment outcomes.[48] The PMT involves evaluating slices at the pons and midbrain regions into three parts—the midline and lateral regions on either side.[48] Similar to PMI, 1 point is assigned when infarcts occupy less than half a region, and 2 points are assigned for greater than half; an additional point is given when the midline is crossed by a large infarction that occupies greater than half the length of the midline of the structure being assessed.[48] This yields a maximum of 5 points in each of the slices, with the recommendation to select the two slices with the highest points between the borders of pons and midbrain, although these two slices do not need to include both the pons and midbrain, per se.[48] At the level of the thalamus, 1 or 2 points are assigned for less than half or greater than half of the thalamus being infarcted on each side, respectively.[48] The PMT can thus range from 0 to 14 (up to 10 points possible for pons and midbrain, up to 4 points for thalamus)[48] (Figure 8). MRI may be of particular utility in AIS involving the posterior circulation given historical limitations of CT-based modalities to identify early ischaemic changes in this territory. However, given the preponderance of CT-based workflows at most centres, Figure 8 provides an application of PMT on a CT for comparison to the PMI in Image 3. It must be emphasized that PMT remains validated on MRI only at this time.[48]

While there is much ongoing investigation of noninvasive imaging of AIS, current guidelines reflect consensus for standardized protocols.[49] Emergent noninvasive imaging of the brain and cervicocerebral arteries in all patients with suspected AIS should be performed expeditiously. In patients presenting greater than 6 h since last know well, perfusion imaging should be performed in the same setting. As such, all patients with AIS should undergo non-contrast CT of the brain and CTA from the aortic arch to vertex. In MRI-based workflows, comparable images should be performed. In CT-based workflows, MRI may be considered for further diagnostic information if needed to arrive at best clinical decisions.[49]

Imaging limitations

As noninvasive imaging has been utilized during the management of patients with AIS, certain long-held assumptions about imaging findings have come under scrutiny. Most prominently, approaches to identifying and measuring core infarct have been the subject of intense debate.[50] As estimates of core volume are routinely incorporated into the therapeutic decisions for AIS patients, it is important to recognize

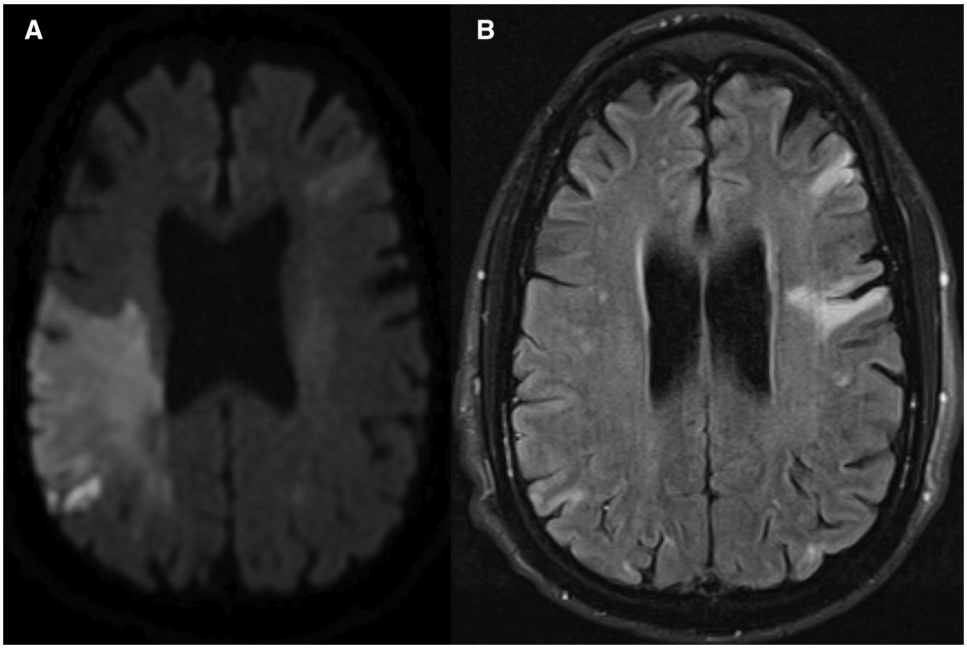

Figure 7. Axial (A) DWI images demonstrate a large right MCA territory area of restricted diffusion. This occupies approximately half of the MCA territory. There is an additional small area of restricted diffusion in the left frontal lobe. (B) FLAIR MR images demonstrate minimal areas of hyperintensity in the right MCA territory. There are areas of FLAIR hyperintensity on the left. Given DWI-FLAIR mismatch, intravenous tPA was administered.

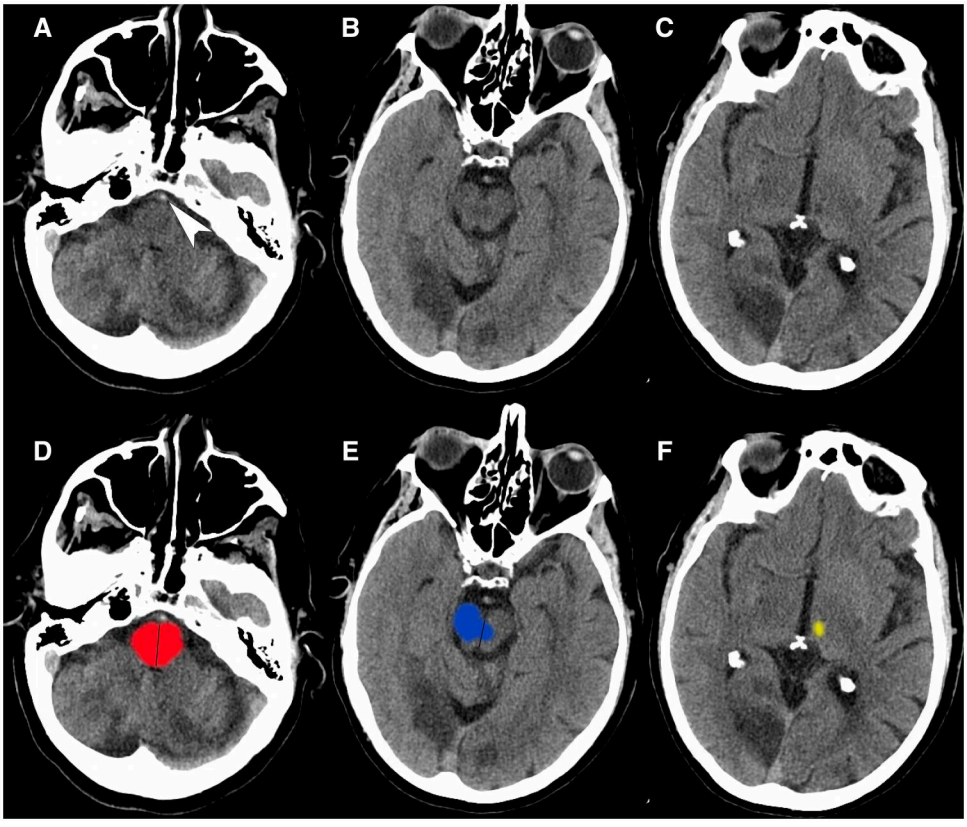

Figure 8. NCCT performed in a patient with acutely altered level of consciousness. Images are shown through the (A) pons, (B) midbrain, and (C) thalamus. Note the hyperdense basilar artery (arrowhead) is noted from the LVO. Annotated versions of the same image are shown below to demonstrate PMT scoring with infarcted areas coloured and midlines delineated in the pons and midbrain for assessing if infarction crossing the midline occupies greater than half that length. (D) The pons scores 5 points for more than half of the pons infarcted on either size and greater than half of the midline affected. (E) The midbrain scores four points for greater than 50% infarcted on the right, less than 50% on the left, and an additional point for greater than half of the midline being affected by infarct. (E) The thalamus scores one point for less than 50% involvement on the left a no involvement on the right. The total of 10 points excludes the patient from mechanical thrombectomy.

limitations. The results of the SELECT2 trial highlight the imprecision of previous assumptions about visualizing irreversible ischaemic damage, ie the core infarct. In this trial, reperfusion demonstrated benefit even in AIS patients with very large estimated cores, and the magnitude of treatment benefit remained even with very small mismatch volumes.[25] Potential explanations for this surprising result include overestimates of core volume based on accepted CBF thresholds, perfusion over-estimation of benign oligemia, benefit assigned to oligemic tissue that ultimately was not at risk, or inclusion of penumbra within tissue labelled as core.[50] Regardless of the mechanism of these findings, there is likely salvageable tissue that is misidentified as core infarct when using prior perfusion algorithms.

Even before the large core trials, thought leaders in AIS treatment challenged the conceptualization of core infarct.[50] They argued that imaging is not able to precisely determine whether or to what extent brain tissue is infarcted or still viable; tissue vulnerability to ischaemia is variable, and a large core volume does not necessarily preclude the presence of tissue that would benefit from reperfusion. They argue that "what we currently call core on early CT or MRI imaging is not actually infarcted tissue but rather a probabilistic estimate of tissue that is highly likely to become infarcted, if fast reperfusion does not occur … The transition from ischaemic core to actual infarction is complex and non-linear."[50] Given the prescience of this exhortation, confirmed by subsequent randomized controlled trial data, the field should reconsider what certain noninvasive imaging findings in the setting of AIS might represent. As discussed above, increased signal intensity on DWI can be partially reversible, particularly in the early time window.[44,51] Additionally, a heterogeneous degree of ischaemia lies within a region with DWI hyperintensity; rather than a binary consideration of normal versus abnormal DWI signal, consideration of apparent diffusion coefficient (ADC) values may be more predictive for identifying irreversible damage.[50,51] Briefly, ADC values reflect the calculation of measured water molecule diffusion within a voxel being interrogated. Utilization of continuous data rather than the forced-dichotomized DWI endpoints may provide a more impactful approach in future care models.

Similar findings have been identified with CT. On NCCT, hypodensity has been considered indicative of infarct. In fact, classic teaching emphasized poor sensitivity for NCCT for detecting acute infarction as it occurs. However, oedema may accompany oligemic but preservable tissue. Hypodensity in the region downstream to an occlusion can be reversible, particularly early in the AIS window.[50] As with DWI, hypodensity is a continuous rather than dichotomous variable. In addition to being subjectively interpreted, hypoattenuation can be affected by vasogenic oedema as opposed to cytotoxic oedema, volume averaging of adjacent structures, and the duration of ischaemia.

Core volume estimates based on perfusion studies are similarly subject to critique. Infarct core has been operationally defined as severely decreased cerebral blood volume or relative CBF. In keeping with the core overestimation trends described above, studies have suggested that perfusion maps can substantially overestimate the ischaemic changes, the so-called ghost core, particularly early in the AIS window.[52,53] All of these trends may lead to withholding MT from patients who would benefit.

These corroborating findings across multiple modalities indicate that the conceptualization of the infarct core should be updated. If a voxel on MRI contains one million neurons, current DWI techniques cannot distinguish between cell death in all neurons versus cell death in some fraction of them.[50] This phenomenon holds for CT-based considerations as well and helps make sense of the results of large core trials that surprised so many. In keeping with these facts, Goyal et al. propose abandoning terms like ischemic core, core infarct, etc.[50] They propose the term severely ischaemic tissue with uncertain viability (SIT-uv).[50] This terminology more adequately describes the volume of tissue that is severely ischaemic but potentially still salvageable if early reperfusion can be achieved.

It is important for diagnostic neuroradiologists to remain up to date on imaging of AIS summarized above to help facilitate the best care for these patients, but it is important to note that this rapidly progressing field is disrupting many previously accepted interpretations of imaging findings. The field of radiology will do well to recognize the limitations of current techniques and concepts, remaining open to future understanding provided by research to further refine management strategies for AIS.

Funding

No funding was received for this study.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

References

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2023 update: a report from the American Heart Association. *Circulation*. 2023;147(8):e93-e621.
2. Osborn AG, Hedlund GL, Salzman KL. *Osborn's Brain: Imaging, Pathology, and Anatomy*. 2nd ed. Elsevier; 2018:1372p.
3. Lyden PD. Cerebroprotection for acute ischemic stroke: looking ahead. *Stroke*. 2021;52(9):3033-3044.
4. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;14(333(24):1581-1587.
5. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008; 359(13):1317-1329.
6. Altersberger VL, Sibolt G, Enz LS, et al. Intravenous thrombolysis 4.5-9 hours after stroke onset: a cohort study from the TRISP collaboration. *Ann Neurol*. 2023;94(2):309-320.

7. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11-20.
8. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019-1030.
9. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372(24):2296-2306.
10. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372(24):2285-2295.
11. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372(11):1009-1018.
12. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723-1731.
13. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet*. 2000;355(9216):1670-1674.
14. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378(1):11-21.
15. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378(8):708-718.
16. Albers GW, Lansberg MG, Brown S, et al. Assessment of optimal patient selection for endovascular thrombectomy beyond 6 hours after symptom onset: a pooled analysis of the AURORA database. *JAMA Neurol*. 2021;78(9):1064-1071.
17. Martins SO, Mont'Alverne F, Rebello LC, et al. Thrombectomy for stroke in the public health care system of Brazil. *N Engl J Med*. 2020;382(24):2316-2326.
18. Mocco J, Siddiqui AH, Fiorella D, et al. POSITIVE: perfusion imaging selection of ischemic stroke patients for endovascular therapy. *J Neurointerv Surg*. 2022;14(2):126-132.
19. Langezaal LCM, van der Hoeven EJRJ, Mont'Alverne FJA, et al. Endovascular therapy for stroke due to basilar-artery occlusion. *N Engl J Med*. 2021;384(20):1910-1920.
20. Liu X, Dai Q, Ye R, et al. Endovascular treatment versus standard medical treatment for vertebrobasilar artery occlusion (BEST): an open-label, randomised controlled trial. *Lancet Neurol*. 2020;19(2):115-122.
21. Tao C, Nogueira RG, Zhu Y, et al. Trial of endovascular treatment of acute basilar-artery occlusion. *N Engl J Med*. 2022;387(15):1361-1372.
22. Jovin TG, Li C, Wu L, et al. Trial of thrombectomy 6 to 24 hours after stroke due to basilar-artery occlusion. *N Engl J Med*. 2022;387(15):1373-1384.
23. Schaefer PW, Yoo AJ, Bell D, et al. CT angiography-source image hypoattenuation predicts clinical outcome in posterior circulation strokes treated with intra-arterial therapy. *Stroke*. 2008;39(11):3107-3109.
24. Yoshimura S, Sakai N, Yamagami H, et al. Endovascular therapy for acute stroke with a large ischemic region. *N Engl J Med*. 2022;386(14):1303-1313.
25. Sarraj A, Hassan AE, Abraham MG, et al. Trial of endovascular thrombectomy for large ischemic strokes. *N Engl J Med*. 2023;388(14):1259-1271.
26. Huo X, Ma G, Tong X, et al. Trial of endovascular therapy for acute ischemic stroke with large infarct. *N Engl J Med*. 2023;388(14):1272-1283.
27. Bendszus M, Fiehler J, Subtil F, et al. Endovascular thrombectomy for acute ischaemic stroke with established large infarct: multicentre, open-label, randomised trial. *Lancet*. 2023;402(10414):1753-1763.
28. Yoo AJ, Zaidat OO. TESLA trial primary results. Munich, Germany; European Stroke Conference, 2023.
29. Costalat V, Lapergue B, Albucher JF, et al. Evaluation of acute mechanical revascularization in large stroke (ASPECTS $\leqslant 5$) and large vessel occlusion within 7 h of last-seen-well: The LASTE multicenter, randomized, clinical trial protocol. *Int J Stroke*. 2024;19(1):114-119.
30. Bendszus M, Bonekamp S, Berge E, et al. A randomized controlled trial to test efficacy and safety of thrombectomy in stroke with extended lesion and extended time window. *Int J Stroke*. 2019;14(1):87-93.
31. Kobeissi H, Adusumilli G, Ghozy S, et al. Endovascular thrombectomy for ischemic stroke with large core volume: An updated, post-TESLA systematic review and meta-analysis of the randomized trials. *Interv Neuroradiol*. 2023;15910199231185738. doi: 10.1177/15910199231185738.
32. Hill DM. A Multicentre, Prospective, Randomized, Parallel Group, Open-label Design to Determine the Efficacy and Safety of Endovascular Thrombectomy for Ischemic Stroke Patients With Symptomatic Acute Medium Vessel Intracranial Occlusions [Internet]. Report No.: NCT05151172. clinicaltrials.gov; 2023. Accessed September 11, 2023. https://clinicaltrials.gov/study/NCT05151172
33. University Hospital, Basel, Switzerland. EnDovascular Therapy Plus Best Medical Treatment (BMT) Versus BMT Alone for MedIum VeSsel Occlusion sTroke—a prAgmatic, International, Multicentre, Randomized triaL (DISTAL) [Internet]. Report No.: NCT05029414. clinicaltrials.gov; 2023. Accessed September 11, 2023. https://clinicaltrials.gov/study/NCT05029414
34. Mohammaden MH, Haussen DC, Nogueira RG. Therapeutic Advancements in the Endovascular Management of Acute Ischemic Stroke. *SVIN*. 2021;1(1):e000168.
35. Puetz V, Sylaja PN, Coutts SB, et al. Extent of hypoattenuation on CT angiography source images predicts functional outcome in patients with basilar artery occlusion. *Stroke*. 2008;39(9):2485-2490.
36. McVerry F, Liebeskind DS, Muir KW. Systematic Review of Methods for Assessing Leptomeningeal Collateral Flow. *AJNR Am J Neuroradiol*. 2012;33(3):576-582.
37. Tong E, Patrie J, Tong S,et al.. Time-resolved CT assessment of collaterals as imaging biomarkers to predict clinical outcomes in acute ischemic stroke. *Neuroradiology*. [Internet]. 2017;59(11). Accessed September 12, 2023. https://pubmed.ncbi.nlm.nih.gov/28864854/
38. Olthuis SGH, Pirson FAV, Pinckaers FME, et al. Endovascular treatment versus no endovascular treatment after 6-24 h in patients with ischaemic stroke and collateral flow on CT angiography (MR CLEAN-LATE) in the Netherlands: a multicentre, open-label, blinded-endpoint, randomised, controlled, phase 3 trial. *Lancet*. 2023;401(10385):1371-1380.
39. Srinivasan A, Goyal M, Al Azri F, Lum C. State-of-the-art imaging of acute stroke. *Radiographics*. 2006;26(Suppl 1):S75-95.
40. Allmendinger AM, Tang ER, Lui YW, Spektor V. Imaging of stroke: part 1, perfusion cT??? Overview of imaging technique, interpretation pearls, and common pitfalls. *AJR Am J Roentgenol*. 2012;198(1):52-62.
41. Murray NM, Culbertson CJ, Wolman DN, Mlynash M, Lansberg MG. Hypoperfusion intensity ratio predicts malignant edema and functional outcome in large-vessel occlusive stroke with poor revascularization. *Neurocrit Care*. 2021;35(1):79-86.
42. Wu RR, Lu SS, Cao YZ, et al. Hypoperfusion intensity ratio correlates with clinical outcome of endovascular thrombectomy in acute ischaemic stroke patients with late therapeutic window. *Clin Radiol*. 2022;77(8):570-576.
43. Guenego A, Fahed R, Albers GW, et al. Hypoperfusion intensity ratio correlates with angiographic collaterals in acute ischaemic stroke with M1 occlusion. *Eur J Neurol*. 2020;27(5):864-870.

44. Thomalla G, Cheng B, Ebinger M, et al. DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4·5 h of symptom onset (PRE-FLAIR): a multicentre observational study. *Lancet Neurol*. 2011;10(11):978-986.
45. Hsia AW, Luby M, Cullison K, et al. Rapid apparent diffusion coefficient evolution after early revascularization. *Stroke*. 2019;50 (8):2086-2092.
46. Inoue M, Mlynash M, Christensen S, et al. Early diffusion-weighted imaging reversal after endovascular reperfusion is typically transient in patients imaged 3 to 6 hours after onset. *Stroke*. 2014;45(4):1024-1028.
47. Campbell BCV, Purushotham A, Christensen S, et al. The infarct core is well represented by the acute diffusion lesion: sustained reversal is infrequent. *J Cereb Blood Flow Metab*. 2012;Jan32 (1):50-56.
48. Liu L, Wang M, Deng Y, et al. Novel diffusion-weighted imaging score showed good prognostic value for acute basilar artery occlusion following endovascular treatment: the pons-midbrain and thalamus score. *Stroke*. 2021;52 (12):3989-3997.
49. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418. cited February 17, 2024. https://www.ahajournals.org/doi/10.1161/STR.0000000000000211
50. Goyal M, Ospel JM, Menon B, et al. Challenging the ischemic core concept in acute ischemic stroke imaging. *Stroke*. 2020;51 (10):3147-3155.
51. Yuh WTC, Alexander MD, Ueda T, et al. Revisiting current golden rules in managing acute ischemic stroke: evaluation of new strategies to further improve treatment selection and outcome. *AJR Am J Roentgenol*. 2017;208(1):32-41.
52. Boned S, Padroni M, Rubiera M, et al. Admission CT perfusion may overestimate initial infarct core: the ghost infarct core concept. *J Neurointerv Surg*. 2017;9(1):66-69.
53. Sivan-Hoffmann R, Saban M, Buxbaum C, et al. Infarct Core Reliability by CT perfusion is a time-dependent phenomenon. *J Neuroimag*. 2020;30(2):240-245.