Stroke

SPECIAL REPORT

Acute Stroke Imaging Research Roadmap IV

Imaging Selection and Outcomes in Acute Stroke Clinical Trials and Practice

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BACKGROUND AND PURPOSE: The Stroke Treatment Academic Industry Roundtable (STAIR) sponsored an imaging session and workshop during the Stroke Treatment Academic Industry Roundtable XI via webinar on October 1 to 2, 2020, to develop consensus recommendations, particularly regarding optimal imaging at primary stroke centers.

METHODS: This forum brought together stroke neurologists, neuroradiologists, neuroimaging research scientists, members of the National Institute of Neurological Disorders and Stroke, industry representatives, and members of the US Food and Drug Administration to discuss imaging priorities in the light of developments in reperfusion therapies, particularly in an extended time window, and reinvigorated interest in brain cytoprotection trials.

RESULTS: The imaging session summarized and compared the imaging components of recent acute stroke trials and debated the optimal imaging strategy at primary stroke centers. The imaging workshop developed consensus recommendations for optimizing the acquisition, analysis, and interpretation of computed tomography and magnetic resonance acute stroke imaging, and also recommendations on imaging strategies for primary stroke centers.

CONCLUSIONS: Recent positive acute stroke clinical trials have extended the treatment window for reperfusion therapies using imaging selection. Achieving rapid and high-quality stroke imaging is therefore critical at both primary and comprehensive stroke centers. Recommendations for enhancing stroke imaging research are provided.

Key Words: angiography ■ clinical trials ■ ischemic stroke ■ perfusion imaging ■ tomography

In 3 years since the previous Stroke Treatment Academic Industry Roundtable (STAIR) X conference, positive trials have extended the time windows for both endovascular thrombectomy (EVT)[1,2] and intravenous thrombolysis.[3–5] These trials used imaging selection to identify patients with a favorable perfusion profile indicating salvageable brain tissue or a magnetic resonance imaging (MRI) diffusion: fluid-attenuated inversion recovery mismatch signature indicating likely onset <4.5 hours in patients with unknown time of symptom onset. Interest in brain cytoprotection was reinvigorated by a prespecified subgroup analysis of the ESCAPE-NA1 trial (Safety and Efficacy of Nerinetide [NA1] in Subjects Undergoing Endovascular Thrombectomy for Stroke) suggesting a 10% absolute benefit in functional independence with nerinetide among patients who did not receive alteplase.[6]

The DAWN trial (Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) used clinical-core mismatch to identify patients with internal carotid and proximal middle cerebral artery occlusion who met small core criteria that varied by age and clinical severity (Table 1).[2] The DEFUSE 3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) used perfusion

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Nonstandard Abbreviations and Acronyms

aOR	adjusted odds ratio
ASPECTS	Alberta Stroke Program Early CT Score
CBF	cerebral blood flow
CT	computed tomography
CTA	CT angiography
CTP	CT perfusion
DAWN	Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo
DEFUSE 3	Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3
ECASS4	European Cooperative Acute Stroke Study-4
EPITHET	Echoplanar Imaging Thrombolysis Evaluation Trial
ESCAPE-NA1	Safety and Efficacy of Nerinetide [NA1] in Subjects Undergoing Endovascular Thrombectomy for Stroke
EVT	endovascular thrombectomy
EXTEND	Extending the Time for Thrombolysis in Emergency Neurological Deficits
FRAME	French Acute Cerebral Multimodal Imaging to Select Patients for Mechanical Thrombectomy
mRS	modified Rankin Scale
PRACTISE	Penumbra and Recanalisation Acute Computed Tomography in Ischaemic Stroke Evaluation
SELECT	Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke
STAIR	Stroke Treatment Academic Industry Roundtable
SWIFT PRIME	Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment
WAKE-UP	Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke

mismatch assessed using computed tomography (CT) or MRI to identify patients with an ischemic core <70 mL, a perfusion mismatch ratio≥1.8, and an absolute mismatch ≥15 mL.[1] There was no evidence of a reduction in treatment effect across the time window used in the trials. As a result, guidelines recommend using these imaging selection paradigms to select patients for EVT in the 6-hour to 24-hour time window.[7–9]

The EXTEND trial (Extending the Time for Thrombolysis in Emergency Neurological Deficits)[4] and meta-analysis[3] with ECASS4 (European Cooperative Acute Stroke Study-4)[10] and EPITHET (Echoplanar Imaging Thrombolysis Evaluation Trial)[11] used perfusion mismatch assessed using CT or MRI to identify patients with an ischemic core <70 mL and perfusion mismatch ratio >1.2 with >10 mL absolute mismatch who could be treated 4.5 to 9 hours after the time they were last known to be well, or <9 hours from the midpoint of sleep for patients with wake-up stroke. Alteplase significantly improved functional outcomes: modified Rankin Scale (mRS) score 0–1 adjusted odds ratio (aOR), 1.86 (1.15–2.99), mRS score 0 to 2 aOR, 1.74 (1.08–2.81) and ordinal analysis common OR, 2.18 (1.41–3.37); with 4.7% symptomatic intracerebral hemorrhage.[3] By comparison, 0- to 3-hour alteplase improved mRS score 0 to 1 with aOR, 1.75 (1.35–2.27). Interestingly, patients who met automated mismatch criteria had strong benefit, whereas there was no evidence of benefit in patients who had visually assessed mismatch but who did not meet automated threshold criteria, although comparison with the automated mismatch group was underpowered and formal statistical interaction was not demonstrated.[3] The WAKE-UP trial (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke) took a different imaging approach and used diffusion–fluid-attenuated inversion recovery mismatch to identify patients with unknown onset time who were likely to be<4.5 hours after stroke onset. This study also demonstrated benefit of intravenous alteplase (mRS score 0–1; aOR, 1.61 [1.09–2.36]).[5] The subgroup of patients with lacunar stroke (ineligible for treatment using perfusion mismatch criteria) appeared to have similar benefit compared with nonlacunar stroke.[12]

Other trials have examined the role of imaging in patient selection, following recommendations in previous Acute Stroke Research Roadmaps.[13–15] The PRACTISE trial (Penumbra and Recanalisation Acute Computed Tomography in Ischaemic Stroke Evaluation), reported in abstract form, randomized 272 patients who presented 0 to 4.5 hours after symptom onset to imaging with either noncontrast CT-only or multimodal CT including CT perfusion (CTP).[16] There was no difference in the time from stroke onset to thrombolysis decision between imaging paradigms. Patients imaged with CTP were less likely to receive thrombolysis (50% versus 69%, OR, 0.38 [95% CI, 0.20–0.71]) but had similar functional outcomes (mRS score 0–1, 52.5% with multimodal CT versus 48.5% with noncontrast CT only, P=0.94), despite the final diagnosis being confirmed as ischemic stroke. This suggests that the withholding of thrombolysis may have been appropriate. The reduction in thrombolysis was seen in mild-moderately affected patients with the most frequent reasons given for withholding thrombolysis being the lack of a vessel occlusion (47%) or perfusion lesion (34%). A large ischemic core was only

Table 1. Imaging Selection Criteria in Trials Extending the Time Window for Reperfusion Therapies

Parameter	DAWN	DEFUSE 3	EXTEND	ECASS4	WAKE-UP
Ischemic core	Diffusion MRI: ADC<620	Diffusion MRI: ADC<620	Diffusion MRI: ADC<620	Diffusion MRI: visual assessment	Diffusion MRI: visual assessment
	CT perfusion: relative CBF<30%	CT perfusion: relative CBF<30%	CT perfusion: relative CBF<30%	N/A	N/A
Critical hypoperfusion	Tmax>6 s	Tmax>6 s	Tmax>6 s	Perfusion MRI: visual assessment	N/A
Mismatch criteria	Clinical-core mismatch (RAPID software): Age>80 years, NIHSS>10, core <20 mL; Age <80 years, NIHSS score 10–19, core<30 mL; age<80 years, NIHSS≥20, core<50 mL	Automated perfusion mismatch (RAPID software): core<70 mL mismatch ratio≥1.8 mismatch volume≥15 mL	Automated perfusion mismatch (RAPID software): core<70 mL mismatch ratio >1.2 mismatch volume >10 mL	Visual perfusion mismatch: core <70 mL mismatch ratio >1.2 mismatch volume >10 mL	Visual diffusion-FLAIR mismatch: Diffusion abnormal without corresponding significant FLAIR hyperintensity
Outcome:	Benefit of EVT 6–24 h	Benefit of EVT 6–16 h	Benefit of IVT 4.5–9 h and 9 h after midpoint of sleep for wake-up stroke	Neutral	Benefit of IVT <4.5 h after symptom discovery for wake-up/unknown onset

ADC indicates apparent diffusion coefficient; CBF, cerebral blood flow; CT, computed tomography; DAWN, Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE 3, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; ECASS4, European Cooperative Acute Stroke Study-4; EVT, endovascular thrombectomy; EXTEND, Extending the Time for Thrombolysis in Emergency Neurological Deficits; FLAIR, fluid-attenuated inversion recovery; IVT, intravenous thrombolysis; MRI, magnetic resonance imaging; N/A, not applicable; NIHSS, National Institutes of Health Stroke Scale; Tmax, time to maximum of the residue function; and WAKE-UP, Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke.

listed as the reason in 3% of patients. The FRAME trial (French Acute Cerebral Multimodal Imaging to Select Patients for Mechanical Thrombectomy) included 218 patients treated with EVT 0 to 6 hours after stroke onset and imaged primarily with perfusion-diffusion MRI.[17] In patients with a mismatch ratio >1.2 and no core volume limit, recanalization was associated with increased functional independence (mRS score 0–2) at 3 months (60% versus 32%, OR, 3.3 [95% CI, 1.2–9.3], *P*=0.02). In contrast, patients without mismatch did not appear to benefit from recanalization (35% versus 45%; OR, 0.64 [95% CI, 0.15–2.7], *P*=0.54). The interaction *P* value for the difference between ORs was 0.06.

The SELECT study (Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke) examined both noncontrast CT and CTP profiles in a prospective cohort of patients with large vessel occlusion imaged 0 to 24 hours after stroke onset to assess the concordance of the two modalities and their correlation with thrombectomy outcomes.[18] The majority (81%) of patients who underwent EVT had favorable profiles both on CT (Alberta Stroke Program Early CT Score [ASPECTS] ≥6) and CTP (ischemic core <70 mL, mismatch ratio ≥1.8, mismatch volume ≥15 mL). The rate of functional independence after EVT was 58% in patients with concordant favorable imaging, compared with 46% in patients with unfavorable CT but favorable CTP and 24% for favorable CT but unfavorable CTP. Additionally, patients with unfavorable CTP had significantly more adverse outcomes, including symptomatic intracerebral hemorrhage, mortality, and neurological worsening, regardless of a favorable noncontrast CT, which may suggest additional value of perfusion imaging in prognostication.

The ESCAPE-NA1 trial tested the PSD95 inhibitor nerinetide in EVT-eligible patients with favorable noncontrast CT and moderate-good collaterals on CT angiography (CTA).[6] Although neutral overall, the prespecified stratum of patients untreated with alteplase had ≈10% absolute benefit in regaining functional independence. Pharmacokinetic data provided biological plausibility for the interaction with alteplase, indicating that alteplase-generated plasmin cleaved nerinetide, reducing nerinetide plasma levels by 50%. The effect of nerinetide in alteplase-ineligible patients will be tested in a further trial but ESCAPE-NA1 provided the first potentially positive brain cytoprotection data in human stroke. This will reinvigorate research into cerebroprotection and requires fresh consideration of the appropriate imaging selection approaches.

ISCHEMIC CORE CONCEPT AND OPERATIONALIZATION

The ischemic core is defined as the brain region that is irreversibly injured at the time of imaging.[14] It may not be histologically infarcted at the time of imaging but cannot be resuscitated, even with immediate reperfusion. This theoretical concept aims to allow the clinician to visualize the best tissue outcome that can be achieved with successful treatment. Various imaging approaches are used to estimate the ischemic core at the time of imaging (rather than predict, which implies a future and conditional state), and they differ in sensitivity, specificity, and interrater reliability. The potential imprecision in estimation of the core has led some to propose an alternative construct of extreme ischemic stress with matching terminology.[19] However, the Stroke Treatment Academic

Industry Roundtable XI consensus is that the concept of the ischemic core remains clinically relevant and alternative terminology is not desirable.

Noncontrast CT hypodensity represents irreversible injury with high specificity but lower sensitivity in the first few hours after stroke onset and interrater agreement for more subtle changes is limited.[20] CTP estimation of the ischemic core can be based on severely reduced relative cerebral blood flow,[21,22] reduced cerebral blood volume,[23] or severely prolonged time to maximum of the residue function.[24] A relative cerebral blood flow (relCBF) threshold<30% of that in normal brain is commonly used by automated software packages and is more sensitive but less specific than the finding of reduced cerebral blood volume.[21,22] If visually assessing a perfusion map, then cerebral blood volume is the preferred estimate of ischemic core because CBF is visually reduced throughout the entire ischemic region, including salvageable penumbral regions. The threshold for irreversible injury using CBF is time dependent. In practice, the time between stroke onset and reperfusion is sufficiently long in most patients for relCBF<30% to reflect irreversible injury.[25,26] However, in patients who present very early after symptom onset and achieve fast reperfusion, a relCBF<30% threshold may overestimate the ischemic core, particularly in white matter.[27] Some studies suggest that in the very early time window (0–90 minutes), a relCBF<20% threshold may produce more accurate volumetric estimates of ischemic core compared with follow-up imaging, but the quality of spatial agreement remains to be determined.[24,28]

There is generally a gradient of CBF reduction and time to maximum of the residue function prolongation across the hypoperfused region. Considering the volumes of tissue with <20% relCBF, in addition to the standard definition of <30% relCBF, can assist the clinician to gauge their level of confidence in CTP-based estimates of ischemic core volume, particularly when there is likely to be a short time window between onset and reperfusion.[24,28] Review of the noncontrast CT in the severely hypoperfused regions may reveal subtle but convincing hypodensity that also reinforces confidence in the extent of ischemic core. There may also be noncontrast CT changes outside the perfusion lesion if partial reperfusion or clot migration has occurred.

Diffusion MRI is highly sensitive for ischemic stroke and becomes abnormal within minutes of the onset of ischemia.[29] Restricted diffusion represents cytotoxic edema and generally reflects permanently injured tissue. However, cytotoxic edema can be reversible in regions with more mildly reduced apparent diffusion coefficient, if reperfusion is rapidly achieved.[30–32] Although some patients have sustained reversal, a temporary reversal in the first hours after reperfusion with subsequent return of abnormal signal by ≈24 hours is also often observed.[33,34] Whether this represents initial tissue recovery and subsequent secondary injury that might potentially be prevented with effective brain cytoprotection directed at late processes such as apoptosis is a key question to address.

Diffusion MRI acquired shortly after CTP formed the reference standard for the derivation of relCBF thresholds for ischemic core using CTP.[21,22] The potential for reversal of diffusion lesions with rapid endovascular reperfusion, therefore, may require recalibration of the CTP thresholds, particularly if effective brain cytoprotective strategies are developed in the future (see recommendations for refinement of ischemic core estimation, Table 2). The potential for collateral blood flow enhancement (eg, sphenopalatine ganglion stimulation[35]) could also shift the relationship between the initial hypoperfusion severity and the ultimate extent of tissue injury. Artificial intelligence approaches that combine multiple parameters and may include clinical variables to estimate the ischemic core are advancing and are likely to outperform simple single-parameter thresholds.

Notwithstanding these caveats, the existing CTP and diffusion MRI thresholds for estimating ischemic core have permitted substantial expansion in treatment time windows in clinical practice. The existing thresholds also had good volumetric agreement with follow-up infarct volume in DEFUSE 3[25] and SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment).[26] As with all diagnostic tests, however, there is imperfect sensitivity and specificity. Physicians, therefore, need to understand the strengths and weaknesses of each imaging tool, synthesize the imaging results with other available information, and use judgment to interpret the data and determine treatment. Having more information is generally positive for clinicians, provided interpretation is sufficiently sophisticated and rapid.

There has been concern that widespread perfusion imaging, particularly in the early time window may lead to exclusion of patients who may potentially benefit from reperfusion therapies. However, this is a challenge of interpretation rather than a flaw in the technique itself. The solution to this problem of over selection likely lies in gaining an improved understanding of the ischemic core volume and location and of the imaging profiles that are associated with benefit from reperfusion. For example, there are multiple subgroup analyses suggesting benefit of reperfusion in selected patients with an estimated ischemic core volume >70 mL (both within and beyond 6 hours after stroke onset).[36–41] The presence of >70 mL core should therefore not be regarded as evidence that benefits from reperfusion is not possible. Instead, it identifies a group of patients in whom the risks and benefits of reperfusion are more finely balanced and ongoing randomized trials may clarify treatment decisions in this group. In addition to ischemic core volume, factors such as lesion location (including involvement of eloquent cortex and tracts), premorbid function and expected

Table 2. Recommendations for Refinement of Ischemic Core Estimation and Optimizing Imaging Acquisition and Processing

Diffusion MRI	CT perfusion	Noncontrast CT
Understanding temporary lesion reversal—is this an opportunity for cerebroprotection to prevent secondary injury?	Recalibration against a refined diffusion MRI definition of core (requires contemporaneous CTP and MRI which has practical challenges) vs follow-up infarct volume in patients with rapid and complete reperfusion	Improved detection of subtle Hounsfield unit changes: High-quality image acquisition Judicious use of iterative reconstruction Further exploration of dual-energy acquisitions Artificial Intelligence detection of subtle changes
Recognition of gradient of tissue injury (nondichotomous tissue fate)	Maps with probabilistic information indicating the degree of confidence in tissue status may aid interpretation	Standardization of assessment of hemorrhagic transformation across CT and MRI modalities
	Artificial intelligence with multiparametric input ± clinical variables is likely to outperform single-parameter thresholds	
Technical pitfalls to consider in analysis of apparent diffusion lesion reversal: Initial infarct edema followed by atrophy Coregistration inaccuracy White vs gray matter differences	Technical pitfalls to consider in analysis of apparent CTP core salvage: Temporary diffusion lesion reversal if follow-up imaging reference is diffusion MRI obtained <24 h Relative insensitivity of noncontrast CT to infarction if used as follow-up reference Coregistration inaccuracy White vs gray matter differences	

CT indicates computed tomography; CTP, CT perfusion; MRI, magnetic resonance imaging.

time to reperfusion warrant consideration when deciding whether to recommend EVT.[36] Physicians should also familiarize themselves with the pitfalls of automated perfusion imaging, many of which are mitigated by review of the unprocessed perfusion source data, familiarity with the locally used processing software and interpretation in the context of noncontrast CT and CTA studies.

There has been concern that the addition of CTP or CTA to a noncontrast CT brain may cause unwarranted delay and worsen patient outcomes. This certainly needs to be avoided. There are examples of systems in which the noncontrast CT is acquired, the patient returns to the emergency room and then has to be sent back to the scanner to acquire CTA, causing unacceptable delays. The capacity to perform a CTA immediately after noncontrast CT 24/7 should be regarded as a requisite skill at any primary stroke center. Once the barriers of intravenous access and technician training to obtain CTA are overcome, the addition of CTP should add only a few minutes (60–70-second acquisition and 2–3 minutes to reconstruct and process perfusion maps with automated software). A review of image acquisition and processing times at 10 primary and 10 comprehensive stroke centers using automated software revealed median time of 2-minute 21 seconds (interquartile range, 1-minute 44 seconds–2-minutes 51 seconds) from first CTP slice to perfusion map availability (Carolina Maier, personal communication). However, the cost of automated processing software is a relevant consideration, particularly for smaller centers.

Although recent trials have studied an approach of omitting intravenous thrombolysis in patients who are able to undergo endovascular thrombectomy immediately upon ED arrival,[42] such an approach is not standard of care at most centers. It, therefore, remains critical that any delay to intravenous thrombolysis is minimized. Ideally, intravenous thrombolysis is commenced in the CT scanner while acquiring additional CTP and CTA imaging, and initial endovascular team or transfer activation occurs on recognition of a proximal hyperdense artery on noncontrast CT.

Visual assessment of imaging using ordinal scales such as ASPECTS and visual collateral grading scales may appear simpler than estimating the volume of ischemic core using CTP or MRI. However, interrater reliability is more limited with visual assessments. Furthermore, the use of visual assessments is most suited to large vessel occlusions, whereas the concept of ischemic core generalizes to all stroke types. The extended window thrombolysis meta-analysis[3] suggested that interrater variability can impact treatment outcomes as patients with visually assessed perfusion mismatch who did not meet automated mismatch criteria appeared not to benefit from thrombolysis. Although the noncontrast CT ASPECTS is sometimes regarded as a more inclusive selection paradigm, excluding patients with low ASPECTS may actually prevent treatment of patients with a relatively small estimated ischemic core using CTP. This can occur because of the unequal volumes of the ASPECTS regions and loss of points due to partial involvement of a region. In the SELECT cohort, 60% of patients with ASPECTS 0-5 had estimated ischemic core volume <50 mL, and these patients appeared to respond favorably to endovascular reperfusion.[18] This potential heterogeneity of treatment effect based on the imaging modality used to identify the extent of ischemic injury will be examined in the ongoing

SELECT 2 randomized trial (https://www.clinicaltrials.gov; Unique identifier: NCT03876457).

OPTIMIZING QUALITY OF MULTIMODAL CT ACQUISITIONS

Noncontrast CT

The noncontrast CT brain remains the key basic investigation for suspected stroke patients and acquisitions must be optimized to minimize artifacts and enhance contrast to noise. The precise parameters required will vary between scanners but sufficient radiation dose is required with careful choice of reconstruction kernel and judicious use of iterative reconstruction. When developing or revising the scan protocol, image quality should be reviewed by a neuroradiologist and radiation physicist. Standard 5-mm thick slices may be complemented by thin (≈1 mm) slice reconstructions to increase sensitivity for hyperdense thrombus in intracranial arteries that is diagnostic of acute ischemic stroke and may indicate a target for EVT even before CTP and CTA acquisition.[43] The images should be reviewed in a range of tissue windows, including the ≈40:40 window width and level settings that maximize the conspicuity subtle hypodensities indicative of early ischemic injury. Dual-energy acquisitions may provide better contrast to noise for assessing subtle parenchymal hypodensity[44] and be useful post-treatment to distinguish contrast staining from hemorrhagic transformation.[45]

CT Perfusion

A minimum *z* axis coverage of 8 cm should be acquired with a strong preference for true whole-brain coverage (≥10 cm) to cover the entire posterior fossa and supratentorial compartments and avoid missing anterior cerebral artery territory and cerebellar perfusion lesions. Standard CTP acquisition protocols use relatively low kV (70–80 kV) to constrain radiation dose while improving sensitivity to iodinated contrast. Slice reconstruction thickness also requires a balance between image noise and spatial resolution with 5-10 mm thick slices generally recommended for perfusion maps. CT protocols require close attention and need to be set up in conjunction with neuroradiologists and medical physicists.[46] Thin (0.5–1.5 mm) slices can be reconstructed to provide time-resolved angiography to assess collaterals and residual flow through a thrombus or critical stenosis. However, further optimization of thin slice reconstruction and processing is required to make this sufficiently rapid to be routinely useful in clinical practice. The duration of acquisition needs to cover the passage of the contrast bolus. Truncated acquisitions risk under-estimation of cerebral blood volume (the area under the time-concentration curve) and, therefore, over-estimation of the ischemic core. In general, 60 seconds provide adequate temporal coverage for most patients if the contrast bolus is injected at high flow rate (eg, 8 mL/s) and with a saline chaser.[47,48]

CT Angiography

Thin slice reconstructions are critical to allow high-resolution multiplanar reformatting and should be routinely stored on PACS systems, despite the volume of data. Dual-energy acquisitions may facilitate bone removal.[49] The assessment of collateral flow on single-phase CTA is prognostic and reliable if good collaterals are visualized. However, accuracy is dependent on the timing of contrast arrival and later-arriving collateral flow can be underestimated, risking exclusion of patients from reperfusion therapies who may benefit. Multiphase CTA (or time-resolved CTA derived from CTP) provides more accurate information on collateral flow and the precise location and extent of arterial occlusion.[50]

IMAGING STRATEGIES AT THE PRIMARY STROKE CENTER

CT is almost exclusively the imaging modality used at primary stroke centers. The establishment of EVT as standard of care treatment for patients with large vessel occlusion means that all primary stroke centers should routinely perform CTA to identify large vessel occlusion. Relying on the clinical severity, as assessed by the National Institutes of Health Stroke Scale, has inadequate sensitivity and specificity for identifying patients with EVT-eligible large vessel occlusions.[51]

Clearly, delays in treatment and transfer need to be avoided and so imaging workflow needs to be streamlined and performed in a single step rather than in separate sessions. In practical terms, this means that scanners need to be equipped with contrast injector pumps and that CT technicians who can perform CTA need to be available 24/7/365. Once CTA is routinely available, the addition of CTP is a relatively minor incremental step. A dedicated Code Stroke imaging protocol that is used routinely and consistently results in better quality scans and fewer technical challenges. Potential benefits and challenges related to acquiring CTP routinely at primary stroke centers are summarized in Table 3.[9,52,53] Key benefits include improved diagnostic accuracy and the potential ability to treat with thrombolysis >4.5 hours after stroke onset. CTP assessment of the ischemic mismatch can also play an important role in identifying which patients are eligible for endovascular therapy and should be transferred for this procedure. It is important that fast image transfer capabilities to the comprehensive stroke center are available, including cloud-based image sharing platforms. The cost of automated processing software

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Table 3. Potential Benefits and Challenges of Acquiring CTP Routinely at Primary Stroke Centers

Benefits	Comment
Increased diagnostic accuracy Reduced treatment of mimics Increased treatment of stroke with atypical clinical presentation	Rapid decisions and limited on-site experience/telemedicine can lead to diagnostic errors and missed treatment opportunities. Artificial intelligence tools for decision assistance and automated alerts about treatable stroke are increasingly available.
Increased diagnostic and prognostic confidence	
Treatment of patients with mild deficits	Risk-benefit assessment in mild stroke is challenging and evidence limited, perfusion lesion/vessel occlusion may inform decision
Treatment of patients with low ASPECTS but small ischemic core	Approximately 60% of patients with ASPECTS 0-5 have ischemic core <50 mL and appear to benefit from reperfusion
Balancing comorbidities and imaging profile when considering potential therapeutic benefit	Patients in practice frequently have comorbidities (not included in clinical trials)—favorable imaging improves likelihood of regaining current quality of life; unfavorable imaging in combination with comorbidities may indicate low probability of treatment benefit
Familiarity that comes with routine acquisition	Faster, less technical errors, improved interpretation with regular use
Potential IV thrombolysis for patients presenting >4.5 h	Evidence of benefit in patients with perfusion mismatch. Recommended in European[53] and Australian[9] but not yet US guidelines. Note that only FLAIR-diffusion MRI mismatch has potential to identify patients with potentially treatable lacunar infarcts with unknown onset
Identify patients likely to meet >6 h endovascular thrombectomy criteria Reduce futile transfers	Cost and dislocation from relatives
Identify patients at risk of large hemispheric infarction	Require transfer to neurosurgical center in case decompressive surgery needed
Aim for a single imaging session without repeating on arrival at comprehensive center	Requires immediate access to CT technician with CT angiography capability. Image transfer to comprehensive center essential.
Challenges	
Technician capability	Skill required is less than for acquiring CT angiography (no bolus timing needed)
Cost of processing software	Particularly relevant to smaller hospitals. Market competition between vendors may lead to reduced cost in future. Costs are potentially offset by reduction in futile transfers and retained reimbursement
Renal Function	Contrast nephropathy has been shown to be rare and reversible[52]
Radiation in the setting of overutilization	Justifiable for diagnostically useful imaging, particularly in patients presenting in an extended time window
Time delay for extra imaging	Delays related to obtaining IV access also apply to CT angiography. CTP acquisition, reconstruction, and processing should take no more than a few minutes if optimally configured. Best practice is to initiate thrombolysis in scanner after CT and before CTP and CTA acquisition.
Unjustified exclusion of patients who may benefit from therapy (over selection)	This risk relates to interpretation rather than acquisition of imaging and requires clinician education to synthesize all available information

ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; CTP, CT perfusion; FLAIR, fluid-attenuated inversion recovery; IV, intravenous; and MRI, magnetic resonance imaging.

for either CTP or automated large vessel occlusion may be a consideration in some settings and the development of open source options would be desirable. However, reducing futile transfers of patients who do not require EVT may offset the software cost and reduce dislocation from relatives.

IMAGING CONSIDERATIONS AT THE COMPREHENSIVE STROKE CENTER

Many of the above considerations also apply at comprehensive stroke centers. A key issue is when to repeat imaging on arrival versus proceed directly to EVT. Repeat imaging can contribute to delayed EVT which may lead to worse functional outcomes.[54] Rapid image transfer from the referring primary stroke center to the receiving comprehensive stroke center is essential to avoid unnecessary repeat imaging. If comprehensive imaging has been performed at the primary center and the time elapsed when the patient arrives at the comprehensive center is not excessive, routinely repeating imaging should not be necessary. The maximum acceptable time before reimaging is required is a key area for future research. Physicians should critically consider what potential findings on repeat imaging would alter their decision to proceed to EVT. In patients who are clinically stable, a primary concern is that the ischemic core may have expanded during transport and that the

patient no longer meets imaging mismatch criteria. If there has been clinical deterioration, hemorrhagic transformation can potentially be excluded via flat-panel CT in the angiography suite. In the scenario of a dramatic clinical improvement, repeat CTA/CTP can be considered if there is strong clinical suspicion of recanalization during transfer. This is more frequent in patients treated with intravenous thrombolysis and if the thrombus is nonocclusive.[55]

For patients presenting directly to a comprehensive center, imaging with multimodal CT or MR is usual. The availability of acute MRI may be particularly useful for wake-up stroke patients as both the perfusion-diffusion and diffusion–fluid-attenuated inversion recovery mismatch paradigms can be used for treatment selection. Some centers are exploring a direct to angiography suite approach. Some angiography suites are equipped with a CT or MRI scanner, whereas others use flat-panel angiography capability to acquire a noncontrast CT. Some angiography equipment can also obtain perfusion images, similar to a standard CT, from the C-arm. The optimal prescreening approach to minimize unnecessary use of scarce angiographic room resources for patients without large vessel occlusion ischemic stroke remains to be determined.

Mobile Stroke Units are employed in some regions and mostly have noncontrast CT and intracranial CTA capability that can differentiate ischemic stroke from intracerebral hemorrhage and identify intracranial large vessel occlusion. Future developments should aim to acquire CTP to permit on-board thrombolysis of extended time window patients and to improve diagnostic accuracy, particularly for more mildly affected suspected stroke patients.

ROLE OF IMAGING IN PATIENT SELECTION AND OUTCOME ASSESSMENT IN FUTURE CLINICAL TRIALS

Brain Cytoprotection

The ideal patient for a brain cytoprotection study has not been determined and may depend on the mechanism of action of the putative agent. A sweet spot for cytoprotective agents might be patients with moderate collaterals who are at risk of infarct expansion before endovascular reperfusion. Patients with excellent collaterals and minimal ischemic core have a good prognosis with reperfusion therapies alone and may not exhibit further benefit with adjunctive therapies. In patients with very poor collateral flow, the delivery of cerebroprotective agents to affected tissue may be insufficient, unless the mechanism of action is compatible with the prevention of injury following reperfusion.

Adjunctive Reperfusion Therapies

Comparative studies of thrombolytics and adjunctive antithrombotic strategies are underway and will likely increase in number as intravenous approaches to reperfusion remain more accessible globally than EVT. As with the comparison of different mechanical reperfusion therapies, these studies may gain statistical power by assessing the surrogate outcome of reperfusion, in addition to functional outcomes that are more susceptible to intercurrent unrelated events and the heterogeneity of ischemic stroke. In patients with large vessel occlusion, the diagnostic angiogram performed before EVT has been used to assess reperfusion after thrombolytic therapy.[56,57] This model has the advantage of being nondisruptive to current time critical standard care. Patients with large and medium vessel occlusion may be the most informative when testing efficacy of reperfusion therapies.[58] As workflow improves, patients presenting directly to endovascular-capable centers may have only a short period from experimental treatment to angiography. Enrollment at spoke sites, particularly rural hospitals, that transfer patients for EVT, and in mobile stroke units, may allow more time for the intervention to have an effect. However, trial design would then need to consider the study coordination resources at spoke sites that are often limited. Comparison of perfusion imaging performed pretreatment and posttreatment can also quantitate the degree of reperfusion (and may substitute for assessment of angiographic reperfusion in patients who do not proceed to angiography for a variety of reasons).

Safety Assessment

Imaging is also relevant to assess safety outcomes, particularly hemorrhagic transformation. The definitions of hemorrhagic transformation have evolved with the Heidelberg classification[59] expanding the ECASS radiological definitions of hemorrhagic infarction versus parenchymal hematoma to include subarachnoid hemorrhage and clinical criteria for substantial deterioration that indicates symptomatic hemorrhagic transformation. Intermodality differences between CT and MRI remain a challenge for reliable classification of hemorrhagic transformation and require further study.

Stroke Treatment Academic Industry Roundtable XI Consensus Recommendations:

1. The concept of ischemic core is clinically relevant and alternative terminology is not desirable. Recommendations for refinement of ischemic core estimation are summarized in Table 2.
2. The speed and quality of multimodal CT acquisitions and post-processing should be optimized (Table 2).
3. CTA should be concurrently obtained with the noncontrast CT scan in suspected stroke patients

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at primary stroke centers. CTP should also be routinely available at primary stroke centers. Potential benefits and challenges of obtaining CT, CTP, and CTA as initial concurrent imaging are summarized in Table 3.

4. Future imaging research:
   i. Determine the scenarios (including acceptable time elapsed) when imaging needs to be repeated in patients transferred for endovascular thrombectomy.
   II. Improve artificial intelligence approaches to estimating ischemic core with CT and MRI.
   III. Determine whether temporary diffusion lesion reversal after reperfusion represents initial tissue recovery and subsequent secondary injury that might potentially be prevented with effective brain cytoprotection.
   IV. Improve prehospital imaging capabilities for triage with or without in-field thrombolysis.
   V. Determine the imaging profile of optimal candidates for brain cytoprotection.
   VI. Refine assessment of hemorrhagic transformation to better account for intermodality differences between CT and MRI.

ARTICLE INFORMATION

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APPENDIX

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