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Multimodal CT in Acute Stroke

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Abstract

Purpose of Review Multimodal CT imaging (non-contrast CT, NCCT; CT angiography, CTA; and CT Perfusion, CTP) is central to acute ischemic stroke diagnosis and treatment. We reviewed the purpose and interpretation of each component of multimodal CT, as well as the evidence for use in routine care.

Recent Findings Acute stroke thrombolysis can be administered immediately following NCCT in acute ischemic stroke patients assessed within 4.5 h of symptom onset. Definitive identification of a large vessel occlusion (LVO) requires vascular imaging, which is easily achieved with CTA. This is critical, as the standard of care for LVO within 6 h of onset is now endovascular thrombectomy (EVT). CTA source images can also be used to estimate the efficacy of collateral flow in LVO patients. The final component (CTP) permits a more accurate assessment of the extent of the ischemic penumbra. Complete multimodal CT, including objective penumbral measurement with CTP, has been used to extend the EVT window to 24 h. There is also randomized controlled trial evidence for extension of the IV thrombolysis window to 9 h with multimodal CT. Although there have been attempts to assess for responders to reperfusion strategies beyond 6 h ("late window") using collateral grades, the only evidence for treatment of this group of patients is based on selection using multimodal CT including CTP. The development of fully automated software providing quantitative ischemic penumbral and core volumes has facilitated the adoption of CTP and complete multimodal CT into routine clinical use.

Summary Multimodal CT is a powerful imaging algorithm that is central to current ischemic stroke patient care.

Keywords CT angiography · CT perfusion · Ischemic stroke · Thrombolysis · Endovascular thrombectomy

Introduction

Multimodal CT in the context of acute stroke assessment refers to the combination of a non-contrast CT (NCCT) scan of the brain, a CT angiogram of the extracranial and intracranial neck vessels, and a CT perfusion scan of the entire brain. Each of the three components of multimodal CT provide unique diagnostic and prognostic information relevant to the management of acute ischemic stroke patients.

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Parenchymal Imaging: Non-contrast CT

NCCT imaging of the brain parenchyma is fundamental to the selection of patients for all acute stroke therapies. In addition to ruling out intracranial hemorrhage, NCCT can also be used to estimate the extent of early ischemic injury. Early NCCT signs of ischemia include sulcal effacement and decreased x-ray attenuation resulting in loss of gray-white matter differentiation. Isolated sulcal effacement reflects venous dilation and elevated cerebral blood volume, which is not always associated with irreversible injury [1]. In contrast, the loss of gray-white matter tissue differentiation indicates cytotoxic edema that results from a failure of ATP-dependent processes within neurons/glia and subsequent cell death. This ultimately results in fluid shifts from the intravascular compartment into the brain parenchyma, reducing tissue density and therefore x-ray attenuation [2, 3]. The rate of this process is highly variable, but always lags behind the changes seen on diffusion-weighted MRI [4, 5]. Nonetheless, NCCT remains the standard initial diagnostic investigation in most stroke centers worldwide due to ease of access and shorter acquisition time.

Assessment of early ischemic changes is highly subjective and inter-rater agreement is often poor. Semi-quantitative rating scales such as the Alberta Stroke Program Early CT Score (ASPECTS) can be used to standardize assessments [6]. The ASPECT score is a negative scale, in which one point is removed for evidence of ischemic change in any of ten different areas supplied by the middle cerebral artery (six cortical regions without distinct borders, labeled M1–M6, insula, caudate, internal capsule, and lentiform nucleus). The ASPECT regions are described on slices at the basal ganglionic and immediate supraganglionic level, which has led to criticism that this only includes approximately 50% of the MCA territory [7]. The ASPECT score is in fact intended to reflect ischemic changes inferior and superior to these two levels, i.e., the entire MCA territory [8]. Although the ASPECT score can be used to quantify the degree of early infarction, scores vary with experience [9]. Any ischemic change within individual ASPECT regions should result in a decrease of 1 point, but this approach is not universally applied, particularly when only a portion of the region is affected. These differences in interpretation of ASPECT scoring rules likely contribute to the relatively poor inter-rater reliability in some studies [10, 11]. Nonetheless, in experienced hands, inter-reliability of ASPECT scoring has been shown to be reasonable and predictive of outcome, as well as response to therapy [8, 9].

Vessel Imaging: CT Angiography

CT angiography (CTA) is a bolus contrast tracking technique that can be used to visualize the macrovasculature from the aortic arch to the cranial vertex within 15 s [12]. Spatial resolution is excellent and in fact superior to most clinical magnetic resonance angiography sequences.

Extracranial Vascular Imaging

Extracranial CTA provides important stroke etiological information, including potential proximal embolic sources such as atheromatous lesions, arterial dissection, aneurysms, and thrombi anywhere from the aortic arch to the base of the skull. It has become the de facto standard of care for imaging the carotid bifurcation, as it allows visualization of extracranial atherosclerotic plaques, demonstrated as luminal irregularity/filling defects, stenosis, or occlusion [13, 14]. Two-dimensional maximum intensity projection (MIP) and three-dimensional multiplanar reconstructed images provide high-resolution angiographic images of the vascular tree that can be useful in determining the need for surgical intervention for carotid disease [12].

Intracranial Vascular Imaging

CTA can be performed immediately following a NCCT and adds minimal time to imaging procedures, permitting efficient imaging of the cerebral vasculature. Identification of an intracranial arterial occlusion on CTA, in the presence of acute focal neurological deficits, generally confirms the diagnosis of acute ischemic stroke. This is a significant improvement over NCCT, as early ischemic changes are not always present, making a normal scan non-diagnostic. Identification of a large vessel occlusion (LVO) is particularly important, given the dramatic treatment effect of endovascular thrombectomy (EVT) in this patient population [15••]. The absence of an occlusion on CTA, however, does not exclude the possibility of an ischemic stroke, as up to 39% of cases are not associated with CTA visible occlusions [16, 17]. These may be related to small vessel disease at the arteriolar level, i.e., lacunar infarcts, or distal occlusions that are below the resolution of CTA [18, 19].

The extent of collateral cerebral blood flow can also be inferred from CT angiographic images. Opacification of smaller vessels distal to but in the territory of the affected artery can often be seen in LVO cases. Although sometimes incorrectly referred to as "collateral vessels," these are in fact smaller branches of the affected cerebral artery, which are being filled by leptomeningeal anastomoses, or pial collateral vessels, which are themselves below the resolution of the CTA [20–23]. The exception to this is collateral flow at the level of the Circle of Willis in the case of distal internal carotid artery occlusions, which are readily visible on CTA. Pial collateral vessels may be anastomotic channels between the smallest branches of adjacent cerebral arteries, i.e., the anterior and middle cerebral artery. They may also represent anastomotic connections between terminal branches of the extracranial and intracranial circulation, i.e., ophthalmic and middle cerebral artery. [23] Collateral flow maintains tissue viability and is the physiological basis for the ischemic penumbra. The presence of collateral flow on CTA is predictive of outcome and response to reperfusion therapy [24, 25]. Regions where blood vessels do not opacify on CTA source images are severely hypoperfused and generally go on to infarct irrespective of treatment. These regions can, therefore, be used to approximate the ischemic core. Delayed filling of vessels occurs in regions that are viable and potentially salvageable (the ischemic penumbra). Assessment of the extent of delay is made difficult by the fact that conventional CTA images are acquired by simultaneous tracking of the contrast bolus temporally and spatially (in an inferior to superior direction). This provides a "snapshot" of vessel filling at one time point, rather than a complete assessment of the dynamic process.

Collateral Grading

The extent of collateral vessel filling on CTA can be assessed qualitatively, i.e., "good" or "poor." As with all subjective

assessments, inter-rater variability is significant and varies with experience [26]. A number of rating systems have been developed in an effort to standardize CTA assessment of collateral flow and improve the selection of patients for treatment (Table 1). Rating or scoring is based on the presence of vessel contrast opacification within the affected cerebral arterial territory [24, 27, 29, 33, 37]. Regional rating of collateral flow, based on an adaption of the ASPECT score, has also been proposed [31].

Multiphase CTA

In conventional CTA, an optimal intravenous contrast bolus profile consists of a rapid rise, plateau of peak enhancement, followed by a rapid fall. Scan acquisition is triggered by contrast bolus-arrival in the aortic arch, which is designed to capture images at the peak arterial enhancement phase [38]. Multiphase CT angiography (mCTA) was developed in an attempt to obtain temporal information by tracking the bolus beyond the peak arterial phase [39]. By repeating the CT acquisition in 1 mm slice increments following a delay of 7–8 s and another 7–8 s, images of the vasculature in the late arterial and venous phases can be obtained (Fig. 1). [35]

mCTA in theory assists in the differentiation of the ischemic core and penumbra. In the peak arterial phase, all hypoperfused territory will demonstrate lack of vessel opacification. Regions in which perfusion is delayed due to supply via collateral vessels will demonstrate vessel opacification in the later phases only. Thus, collateral flow can be more accurately demonstrated with mCTA. Collateral grade scoring systems have become increasingly complex [35, 36]. The most recent iteration has gone beyond grading of simple opacification of vessels to include regional delay of filling between phases, the extent of filling, and the delay of contrast washout in the late phases. Interestingly, the investigation of regional grading indicates that delayed washout in the late CTA phase is associated with poor outcome, which contrasts with other rating systems where persisting vessel opacification is considered to be consistent with a good collateral flow pattern (Fig. 1) [36]. These variables have been hypothesized to correspond to changes in local perfusion pressure and provide information that is similar to that obtained with CT perfusion (CTP) [34–36, 40]. There are limited data supporting the use of multiphase CTA as a selection tool for reperfusion therapies. In the ESCAPE trial, 195/314 (62%) of patients were assessed with mCTA. In all other reperfusion therapy trials, single-phase CTA was used to guide patient selection. Comparative studies also suggest that mCTA may not appreciably change outcome or treatment selection over conventional CTA [41, 42]. The most significant limitation of mCTA, however, is that it allows assessment only of the macrovascular vessels. In order to demonstrate changes at the tissue level, an assessment of the microcirculation is required.

CT Perfusion

CTP imaging is a kinetic tracer technique similar to CTA. Unlike the latter, however, CTP also tracks the bolus of contrast over time [1, 43–52]. The change in signal intensity resulting from contrast arrival in the tissue, measured in Hounsfield units, is proportional to the concentration of contrast at each time point, allowing time-density curves to be generated for each voxel (Fig. 1). Perfusion parameters can then be derived from the tissue-time density curve, based on the central volume principle, and used to generate maps of regional (*r*) CBV, CBF, and time to peak (TTP). CBF is proportional to the amplitude of the curve and CBV to the area under the curve [53, 54]. As these measurements are made on a voxel-wise level and are sensitive to relatively small changes in the tissue signal, which provides an assessment of the microcirculation. This makes it possible to demonstrate focal ischemia below the resolution visualized with CTA. This is particularly important in cases of non-large vessel occlusion [55–58].

Errors inherent in the acquisition due to delay and dispersion of the intravenous bolus are corrected for mathematically, most often using a deconvolution algorithm and a known arterial time-density curve (the arterial input function). Depending on the algorithm used, different time domain maps, such as Tmax or delay time (DT), can also be produced. These are essentially corrected TTP maps. In order to obtain quantitative CBF and CBV values, it is necessary to scale images to a region where CBV is known, i.e., an intravascular space—generally a venous sinus (the venous output function). Mean transit time (MTT) maps can also be calculated as the ratio of CBV/CBF after correction.

CTP maps qualitatively demonstrate the tissue at risk for infarction as well as the extent of the ischemic core (Fig. 1). Areas where CBF and CBV are very low are seen in non-viable/non-salvageable tissue and correspond to the core. Regions where flow is lower than contralateral homologous regions, but not part of the core, are defined as penumbral [1, 45–51]. Penumbral tissue is sometimes described as areas of "mismatch," where TTP/Tmax/DT are prolonged, but CBF and CBV are partially maintained.

Given the necessity for speed in treating ischemic stroke patients, qualitative and semi-quantitative assessments were utilized in earlier perfusion based selection studies [59–61]. The fact that thresholds for ischemic infarction are time-dependent has also made defining the ischemic core and penumbra based on perfusion measurements challenging [62]. Over the last decade, considerable progress has been made in this area. An increasingly accepted definition of an ischemic penumbral pattern is a volume of hypoperfused tissue > 15 ml and an infarct core volume < 70 ml. Significantly hypoperfused tissue volume is defined as that with Tmax > 6 s or delay time > 3 s. Infarct core is defined by using a "double threshold" of Tmax > 6 s (or delay time > 3 s) and a

Table 1 CT angiographic collateral grading systems for acute ischemic stroke

Kim [27][a]	ASITN [28]	Miteff [24]	Maas [29]	Lima [30]	Menon (ASPECTS) [31][b]
Grade 0 • Absence of capillary blush in ischemic site	Grade 0 • No visible collateral	Poor • Superficial distal vessel filling	Grade 1 • Absent collaterals	Grade 1 • Less than contralateral side	Poor • Score of ≤ 10
Grade 1 • Collaterals to the periphery of ischemic site	Grade 1 • Slow collaterals to the periphery of the ischemic site	Moderate • Vessels seen at the Sylvian fissure	Grade 2 • Less than contralateral side	Grade 2 • Equal to contralateral side	Intermediate • Score of 11–16
Grade 2 • Complete irrigation of ischemic site via collaterals	Grade 2 • Rapid collaterals to the periphery of ischemic site and a portion of the ischemic territory	Good • Vessel filling in entire MCA distal to the occlusion	Grade 3 • Equal to contralateral side	Grade 3 • Greater than contralateral side	Good • Score of 17–20
Grade 3 • Normal, anterograde flow	Grade 3 • Slow but complete blood flow to the ischemic site		Grade 4 • Greater than contralateral side		
	Grade 4 • Rapid complete blood flow to the entire ischemic territory by retrograde perfusion		Grade 5 • Exuberant		

Tan [32]	Yeo [33]	Demchuk (ESCAPE) [34]	Menon (CTA) [35]	Menon (mCTA) [35]	D'esterre [36][c]
Absent • Absent collateral supply to the occluded MCA territory	Absent/Poor • Collateral supply filling < 50% of ischemic site	Absent/Poor • Collateral supply filling < 50% of the occluded MCA territory	Grade 0—Poor • No visible vessels in ischemic territory	Grade 0—Poor • No visible vessels in ischemic territory	Poor 1. No washout 2. 2 phase delay of peak 3. 0–50% collateral filling
Poor • Collateral supply filling ≤ 50% but > 0% of the occluded MCA territory	Moderate/Good • Collateral supply filling ≥ 50% of ischemic site	Moderate • Collateral supply filling ≥ 50% but < 100% of the occluded MCA territory	Grade 1—Poor • Few vessels visible in the occluded vascular territory	Grade 1—Poor • Few vessels visible in the occluded vascular territory in any phase	Moderate 1. Delayed/incomplete washout 2. 1 phase delay of peak 3. 50–99% collateral filling
Moderate • Collateral supply filling > 50% but < 100% of the occluded MCA territory		Good • 100% collateral supply of the occluded MCA territory	Grade 2—Moderate • Decreased prominence and extent and regions with no vessels in the ischemic territory of the affected hemisphere	Grade 2—Moderate • 2 phase delay with decrease in extent and prominence OR • 1 phase delay with regions lacking any vessels	Good 1. Complete washout 2. No Phase delay of peak 3. Normal collateral filling
Good • 100% collateral supply of the occluded MCA territory			Grade 3—Moderate • moderately reduced prominence and extent of pial vessels in the ischemic territory	Grade 3—Moderate • 2 phase delay OR • 1 phase delay with significantly reduced number of vessels filling	
			Grade 4—Good	Grade 4—Good	

Table 1 (continued)

	• Slightly reduced prominence and extent of pial vessels in the ischemic territory Grade 5—Good • Normal pial vessel enhancement	• 1 phase delay with normal prominence and extent Grade 5—Good • Normal pial vessel enhancement, no delay

[a] A score between 0 and 3 is assessed for 15 different vascular territories guided by the ASPECT scoring system

[b] Scores are given based on the ASPECT scoring system. M1–M6, ACA, and the basal ganglia are given a score of either 0 (artery not seen), 1 (artery less prominent than contralateral side), or 2 (arterery equally or more prominent than contralateral side). The sylvian sulcus is also given a score of 0 (artery not seen), 2 (artery less prominent than contralateral side), or 4 (artery equally or more prominent than contralateral side)

[c] A score between 1 and 3 is given for each parameter: delay, extent, and washout

ACA anterior cerebral artery, *ASPECTS* Alberta Stroke Program Early CT Score, *CTA* computed tomography angiography, *MCA* middle cerebral artery, *mCTA* multiphase CTA

relative (to the contralateral hemisphere) CBF of < 30% [63, 64]. These definitions of core and penumbra have been validated and demonstrated to predict outcomes as well as the response to thrombolytic therapy in a large international registry [65]. A penumbral pattern has also been found to be predictive of a good response to treatment in a post-hoc analysis of patients included in an EVT trial [66•].

In addition to the pathophysiological challenges of defining the penumbra described above, the complex and time-consuming nature of post-processing has hampered efforts to bring perfusion imaging into the clinical mainstream. In the past, penumbral patterns were identified subjectively as areas of "mismatch," where Tmax (or delay time) was prolonged, but CBF and CBV were partially maintained. Quantitative penumbral and core volumes could be measured "offline," using manual thresholding and planimetric techniques, but not in real time. Physicians unfamiliar with the various CTP maps were reluctant to make rapid clinical decisions based on a complex array of imaging information. Early attempts at simplifying the approach to CTP assessment by applying the ASPECT scoring system to perfusion maps were not adopted widely [59]. More recently, these problems have been resolved with the development of third-party software platforms capable of automating the deconvolution, calibration, thresholding, and volume measurement processes [67, 68]. This results in an operator-independent measurement of the total at risk, penumbral, and ischemic core volumes. The clinician is presented with a very straightforward risk map, which is a visual representation of the ischemic core and penumbra. Risk maps remove the complexities of interpreting multiple CTP parameter maps simultaneously, which can be challenging for non-experts. In addition to the prognostic information important to treatment selection, CTP is often diagnostic in the acute setting, particularly when a proximal LVO is not present [55–58].

Although the iodinated contrast media can be associated with acute kidney injury (contrast induced nephropathy; CIN), the risk does not appear to be significantly increased using multimodal CT protocols [69]. There is no evidence that CIN occurs in patients with estimated glomerular filatration rates > 30 ml/min. Although the risk of further injury in patients with known baseline renal dysfunction must be weighed against the benefits of a definitive diagnosis that can be treated in individual patients, routine screening is not recommended prior to multimodal CT in acute stroke patients [70].

Multimodal CT in Reperfusion Trials

Patients with a large ischemic penumbra and small infarct core are the ideal candidates for acute treatment, irrespective of time from onset [71]. Over time, stroke treatment trials have evolved from utilizing simple parenchymal imaging alone to full multimodal CT for assessment of patient eligibility (Table 2). The original thrombolysis studies did not utilize

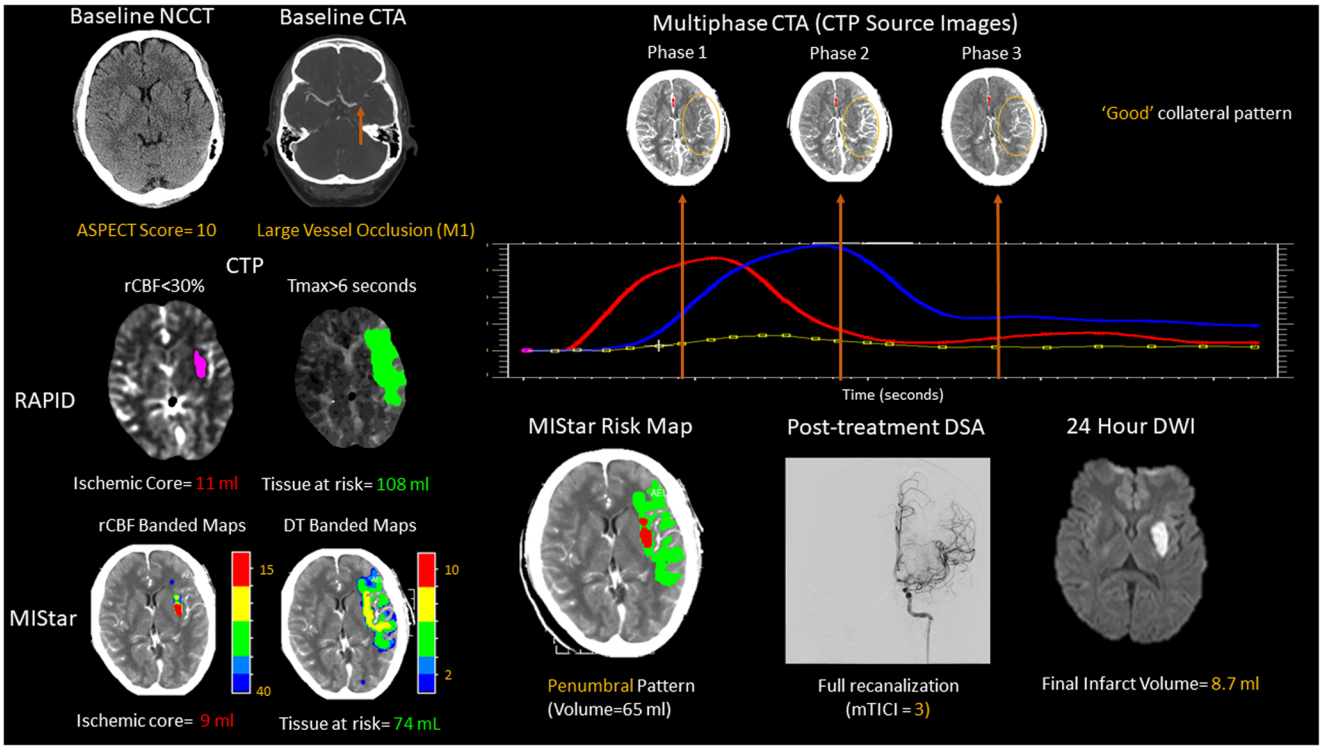

Fig. 1 Multimodal CT obtained in a 74-year-old male at 7.5 h after stroke onset. The NCCT shows no evidence of parenchymal early ischemic change (Alberta Stroke Program Early CT Score, ASPECTS = 10). Occlusion of the M1 segment of the left middle-cerebral artery (MCA) is demonstrated on the CT Angiogram (CTA). Multiphase CTA obtained from CTP source images suggests good collateral flow, although delayed late phase washout has been associated with poor outcome (see text). CT perfusion (CTP) images were post-processed using both the MIStar and RAPID software. Both programs utilize a double threshold approach to ischemic core definition, based on a relative cerebral blood flow (rCBF) of < 30%, within an area at risk defined by contrast delay. The larger penumbral volume reported with RAPID (108–11 = 97 ml) than MIStar is related to differences in deconvolution algorithms and the time domain parameter utilized to define tissue at risk (delay time (DT) = 74.0 ml (MISTAR) cf. Tmax = 108 ml (RAPID)). Successful recanalization (thrombolysis in cerebral infarction; TICI grade 3) was associated with a 24 h infarct volume and topography comparable to the ischemic core predicted by both RAPID and MIStar

penumbral imaging to select patients for treatment. A non-contrast CT was used largely to exclude patients presenting with ICH or extensive early infarction [72–74]. Despite the absence of advanced imaging, the pivotal NINDS trials showed a strong benefit for alteplase treatment initiated within 3 h of stroke onset [72]. This non-selective approach was later shown to be effective up to 4.5 h after onset, although with an increased number needed to treat in the 3–4.5 h window [79]. This likely reflects the fact that most patients within this early time window have penumbral patterns. The proportion of patients with penumbral patterns decreases rapidly over time, but symptom duration is an imperfect surrogate for the presence and extent of the ischemic penumbra. Recent CTP studies have demonstrated that many patients do not have penumbral tissue even when imaged within 3 h [59, 60, 93••, 95]. These same studies have shown that many patients have significant penumbral tissue persisting well beyond 3 h after stroke onset.

All of the successful EVT trials have been completed using CTA to demonstrate an LVO. This approach was highly successful within 6 h of onset. This time window was studied almost exclusively in the five pivotal EVT trials, which included 1287 patients [34, 83–86]. Only 78 patients were randomized more than 6 h after onset in 2 of the trials [34, 84]. The majority of patients enrolled in the pivotal EVT trials were randomized and treated on the basis of this truncated form of multimodal imaging, which required demonstration of an LVO and an absence of extensive early infarct changes on NCCT. One of the trials (ESCAPE) also required a moderate-good collateral grade [34]. The only LVO treatment trial that required a complete multimodal assessment was the EXTEND-IA trial [85]. Eligible patients all had evidence of an ischemic penumbral pattern on CTP, in addition to an LVO, prior to randomization, i.e., a "dual target." Despite the fact that EXTEND-IA was the smallest of the five trials assessing EVT within 6 h of onset, the treatment effect was the largest (31% absolute increased rate of functional independence over alteplase alone). This may reflect the improved selection of patient responders, on the basis of penumbral patterns. Although not required, CTP was in fact obtained in many patients included in the other four HERMES trials. Post-hoc analysis of the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial (138 of 316 patients underwent CTP) suggested that most patients had a penumbral pattern (90.6%) [66•]. Non-penumbral patterns were associated with a poorer outcome, although a response to EVT could not be

Table 2 Multimodal CT imaging criteria in stroke treatment trials

Trial	Time window	Intervention/Control	Sample size	Treatment effect (good clinical outcome)[a]	NCCT	CTA required	CTP required (software used)	Advanced imaging criteria
NINDS [72]	0–3 h	IV r-tPA/placebo	333	+ 13%	✓			
ECASS [73]	0–6 h	IV r-tPA/placebo	511	+ 12%	✓			
ECASS 2 [74]	0–6 h	IV r-tPA/placebo	800	+ 8.9%	✓			
PROACT [75]	0–6 h	Intra-arterial Pro-UK	105	+ 2%	✓			
ATLANTIS [76]	3–5 h	IV r-tPA/placebo	547	+ 8%	✓			
PROACT- 2 [77]	0–6 h	Intra-arterial Pro-UK	180	+ 15%	✓			
MELT [78]	0–6 h	Intra-arterial UK	114	+ 10%	✓			
ECASS 3 [79]	3–4.5 h	IV r-tPA/placebo	730	+ 7%	✓			
IST 3 [80]	0–6 h	IV r-tPA/standard of care	3035	+ 2%	✓			
IMS-3 [81]	0–3 h	EVT/standard of care	656	+ 3%	✓			
ATTEST [82]	0–4.5 h	IV TNK/r-tPA	104	− 3%	✓	[b]	[b]	
MR CLEAN [83]	0–6 h	EVT/standard of care	500	+ 12%	✓	✓		LVO
REVESCAT [84]	0–8 h	EVT/standard of care	206	+ 16%	✓	✓		LVO
EXTEND-IA [85]	0–4.5 h	EVT/standard of care	70	+ 31%	✓	✓	✓ (RAPID)	LVO + Penumbra (Tmax > 6 s); Core > 70 ml (rCBF < 30% AND Tmax > 6 s); absolute difference of 10 mL between core and penumbra
SWIFT PRIME [86]	0–4.5 h	EVT/standard of care	196	+ 24%	✓	✓	***	LVO
ESCAPE [34]	0–12 h	EVT/standard of care	315	+ 22%	✓	✓		Moderate–Good collaterals (> 50% of contralateral side)
THRACE [87]	0–4 h	EVT/standard of care	402	+ 11%	✓	✓		LVO
THERAPY [88]	0–4.5 h	EVT/standard of care	108	+ 8%	✓	✓		LVO
PISTE [89]	0–4.5 h	EVT/standard of care	65	+ 12%	✓	✓		LVO
NOR-TEST [90]	0–4.5 h	IV TNK/r-tPA	1107	+ 1%	✓			
EXTEND-IA TNK [91]	0–4.5 h	IV TNK pre EVT	202	+ 13%	✓	✓	✓ (RAPID)	Penumbra (Tmax > 6 s); Core > 70 ml (rCBF < 30% AND Tmax > 6 s); Total at risk:core > 1.8; absolute difference of 10 ml between core and penumbra
DEFUSE-3 [92••]	6–16 h	EVT/ standard of care	182	+ 28%	✓	✓	✓ (RAPID)	Penumbra < 15 ml (Tmax > 6 s); Core > 70 ml (rCBF < 30% AND Tmax > 6 s); Total at risk: core > 1.8

Table 2 (continued)

Trial	Time window	Intervention/Control	Sample size	Treatment effect (good clinical outcome)[a]	NCCT	CTA required	CTP required (software used)	Advanced imaging criteria
DAWN [93••]	6–24 h	EVT/ standard of care	206	+ 33%	✓	✓	✓ (RAPID)	Group A: < 21 mL; group B: < 31 ml; group C: 31-51 ml
EXTEND [94••]	4.5–9 h	IV r-tPA/placebo	225	+ 6.7%	✓	✓	✓ (RAPID)	Penumbra (Tmax > 6 s); Core > 70 ml (rCBF < 30% AND Tmax > 6 s); Total at risk:core > 1.8; absolute difference of 10 ml between core and penumbra
TIMELESS[d]	4.5–24 h	IV TNK/placebo	456	In progress	✓	✓	✓ (RAPID)	Penumbra < 15 ml (Tmax > 6 s); Core > 70 ml (rCBF < 30% AND Tmax > 6 s); total at risk:core > 1.8
TASTE[e]	0–4.5 h	IV TNK/r-tPA	Estimated 700	In progress	✓	✓	✓ (MIStar)	Penumbra < 15 ml (DT > 3 s); Core > 70 ml (rCBF < 30% AND DT > 3 s); total at risk:core > 1.8

CTA computed tomography angiography, *CTP* computed tomography perfusion, *DT* delay time, *EVT* endovascular therapy, *IAT* aspiration thrombectomy, *IV* intra-venous, *LVO* large-vessel occlusion, *mRS* modified Rankin Score, *NCCT* non-contrast computed tomography, *OHS* Oxford Handicap Scale, *rCBF* relative cerebral blood flow, *r-tPA* tissue plasminogen activator (alteplase), *Tmax* time-to-maximum, *TNK* tenecteplase, *UK* urokinase

NINDS National Institute of Neurological Disorders and Stroke, *ECASS* European Cooperative Acute Stroke Study, *ECASS II* Randomized Double-blind Placebo-controlled Trial of Thrombolytic Therapy With Intravenous Alteplase in Acute Ischaemic Stroke, *PROACT* Prolyse in Acute Cerebral Thromboembolism; *ATLANTIS* Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; *PROACT II* Prolyse in Acute Cerebral Thromboembolism II; *MELT* Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial; *ECASS III* European Cooperative Acute Stroke Study III: A Placebo Controlled Trial of Alteplase (Rt-PA) in Acute Ischemic Hemispheric Stroke Where Thrombolysis is Initiated Between 3 and 4 Hours 30 Minutes After Stroke Onset; *IST 3* Third International Stroke Trial; *IMS-3* Interventional Management of Stroke 3; *ATTEST* Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis; *MR CLEAN* Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; *REVESCAT* Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; *EXTEND-IA* Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial; *SWIFT PRIME* Solitaire™ With the Intention For Thrombectomy as Primary Endovascular Treatment; *ESCAPE* Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; *THRACE* Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke; *THERAPY* Assess the Penumbra System in the Treatment of Acute Stroke; *PISTE* Pragmatic Ischaemic Stroke Thrombectomy Evaluation; *NOR-TEST* Study of Tenecteplase Versus Alteplase for Thrombolysis (Clot Dissolving) in Acute Ischemic Stroke; EXTEND-IA TNK–Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke; *DEFUSE 3* Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; *DAWN* Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention; *EXTEND* Extending the Time for Thrombolysis in Emergency Neurological Deficits; *TIMELESS* Prospective, Double-blind, Randomized, Placebo-controlled Trial of Thrombolysis in Imaging-eligible, Late-window Patients to Assess the Efficacy and Safety of Tenecteplase; *TASTE* Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation

[a] Good functional outcome was defined as an mRS of 0–2, except in the cases of the NINDS and PROACT trial that used an mRS of 0–1, and the IST trial that used an OHS of 0–2

[b] CTA and CTP were acquired for retrospective analysis but were not used to guide randomization

[c] CTP required for the first 71 patients. CTP was encouraged but not required for final 125 patients to accommodate sites with limited CTP capabilities

[d] TIMELESS ClinicalTrials.gov number, NCT03785678

[e] TASTE anzctr.org number, ACTRN12613000243718, sample size estimated due to adaptive trial design

ruled out, given the small number of patients. Another post-hoc analysis of seven major endovascular trials (MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, REVASCAT, PISTE, and THRACE—acronyms defined in Table 2) included 591 of 1764 patients who underwent CTP prior to randomization to EVT/standard therapy [95]. Although this analysis suggested some treatment benefit, even in patients with large cores, the odds of independent recovery decreased by 23% with every 10 ml increase in the core volume measured with CTP even in patients successfully treated with EVT [95]. Within 6 h of onset therefore, CTP identification of large cores may help temper expectations of the response to EVT.

In patients presenting more than 6 h after onset, the only available evidence for treatment with EVT is based on a complete multimodal assessment including CTP. The diffusion-weighted imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) trial randomized patients with acute ischemic stroke, CTA evidence of an LVO and salvageable brain 6–24 h after symptom onset (Table 2). The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3) trial included patients between 6 and 16 h after onset with CTA evidence of an LVO and a CTP penumbral pattern. In both the DAWN and DEFUSE trials, an objective measurement of ischemic core volume based on pre-defined thresholds and an automated post-processing algorithm were used (Table 2) [92••, 93••].

Multimodal imaging including CTP-based penumbral measurements has also been used to extend the treatment window for thrombolysis up to 9 h. The Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial randomized patients with ischemic stroke between 4.5 and 9 h of the last known well time (65% were wake up). Patients were randomized to alteplase or placebo. Alteplase significantly improved the odds of a good functional outcome in this relatively late time window [94••]. In addition, a meta-analysis of 414 patients from the EXTEND, the European Cooperative Acute Stroke Study 4 (ECASS 4), and the Echolplanar Imaging Thrombolysis Evaluation Trial (EPITHET) trials (both of which utilized MRI to identify visually estimated penumbral patterns) indicated that alteplase in the 4.5–9 h window was associated with an absolute increase in the rate of excellent functional outcome (mRS 0–1 at 90 days) of 10% (36% versus 26% of patients with objective penumbral patterns, $p = 0.012$) [96, 97, 98••].

Evidence Gaps and Ongoing Trials

It is unknown if thrombolysis candidates can also be selected on the basis of penumbral imaging in the very late time window (9–24 h after onset). It is biologically plausible that these patients will respond to lytic reperfusion therapy as well. Certainly, the evidence from the EXTEND, ECASS-4, and EPITHET trials suggests that patients with penumbral patterns do respond to thrombolytic therapy up to 9 h after onset, although it remains to be seen if this will change practice guidelines [98••]. The ongoing Prospective, Double-blind, Randomized, Placebo-controlled Trial of Thrombolysis in Imaging-eligible, Late-window Patients to Assess the Efficacy and Safety of Tenecteplase (TIMELESS ClinicalTrials.gov number, NCT03785678) trial is testing the hypothesis that patients presenting 4.5–24 h after onset with a penumbral pattern will benefit from thrombolysis with the novel agent tenecteplase. Unlike the EXTEND trial, patients are eligible for EVT following randomization to tenecteplase or placebo. All patients are screened with full multimodal CT and must have a dual target of vessel occlusion on CTA and objective penumbral on CTP (Table 2). Another ongoing trial, the Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation (TASTE anzctr.org number, ACTRN12613000243718) Trial, is testing the hypothesis that tenecteplase is superior to alteplase within 4.5 h is also using CTP defined penumbral imaging to select patients.

Multimodal CT in Clinical Care: Current Practice Patterns

Current guidelines recommend treatment of all patients with ischemic stroke symptoms and disabling deficits who present within 4.5 h of onset be treated with intravenous alteplase without delay immediately after NCCT, provided no blood or extensive early ischemic changes are identified [13]. Identification of an LVO requires a CTA, which has resulted in the common practice of administering a bolus of alteplase immediately after the NCCT head is obtained and while the patient remains on the CT table. This ensures rapid treatment while allowing the assessment process to continue. It is critical, however, that the infusion begins immediately after the tPA bolus, in order to avoid a drop to pre-bolus lytic activity levels [99].

Once the tPA infusion is running, a CTA can be obtained. In many centers, the assessment may stop here and the decision on whether to proceed to EVT is based entirely on the appearance of the NCCT and the CTA. This practice pattern is certainly supported by the available evidence in patients presenting within 6 h of onset. All evidence for selection of patients for EVT between 6 and 24 h after onset is based on complete multimodal imaging including CTP. Although it has been advocated that patients presenting in the "late window" (6–24 h after onset) can be selected for EVT on the basis of NCCT and CTA alone, this approach is an unproven extrapolation of available evidence [100]. Current guidelines do

not support this approach and clearly state a complete multimodal CT including CTP is required to assess EVT candidates in this late treatment window [13, 70, 101, 102].

The evidence for treatment response based on differential methods of imaging assessment depending on the time from symptom onset has led to variable practice patterns. In some centers, the choice of imaging is based on time to presentation, where CTP is reserved for late-presenting patients only. In primary stroke centers, the assessment may be limited to NCCT only, with multimodal imaging completed only after transfer to comprehensive referral centers. Increasingly, referral is based on the presence of LVO identified after CTA at the primary center. In other centers, a more universal approach to stroke assessment, with immediate multimodal imaging in all cases of suspected stroke. Although this does increase the total time required to assess patients, it also provides an immediate assessment of the state of both the intracranial and extracranial vasculature, as well as the cerebral tissue at the microvascular level. Furthermore, the EXTEND results suggest additional treatment responders to alteplase can be identified using CTP up to 9 h after onset. Although treatment guidelines have not yet changed, this evidence further supports the use of full multimodal CT imaging assessment of all stroke patients. Aside from the selection of patients for treatment, CTP is a highly sensitive diagnostic tool, second only to diffusion-weighted MRI. One practical issue is that objective ischemic core and penumbra volume measurements are currently available only with relatively expensive third-party software, which may be an issue particularly in low–middle-income countries. This can lead to use of the more subjective hardware vendor supplied maps, with subsequent errors in patient selection. In time, however, it is likely that vendor-provided software will also improve and include objective volume measurements.

Conclusions

Multimodal CT is an ideal acute stroke imaging tool that has become the standard of care in many centers around the world. The accessibility of this technology means that it can be acquired in both primary and comprehensive stroke centers in order to rapidly diagnose and prognosticate acute ischemic stroke patients. CT angiography and perfusion provide complementary information useful for treatment selection. Recent improvements in standardization and objective volume assessment have made CT perfusion approachable and useful for clinicians less experienced with the technique.

Compliance with Ethical Standards

Conflict of Interest Dr. Wannamaker reports a grant from the Quality Improvement & Clinical Research Alberta Stroke Program, during the conduct of the study. Dr. Buck declares no potential conflicts of interest. Dr. Butcher has served as an advisory board consultant and received speaker's fees and investigator-initiated grant support from Boehringer-Ingelheim, Bayer, BMS-Pfizer and Servier.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Butcher KS, Lee SB, Parsons MW, Allport L, Fink J, Tress B, et al. Differential prognosis of isolated cortical swelling and hypoattenuation on CT in acute stroke. Stroke. 2007;38(3):941–7.
2. Dzialowski I, Weber J, Doerfler A, Forsting M, von Kummer R. Brain tissue water uptake after middle cerebral artery occlusion assessed with CT. J Neuroimaging. 2004;14(1):42–8.
3. Schramm P, Schellinger PD, Fiebach JB, Heiland S, Jansen O, Knauth M, et al. Comparison of CT and CT angiography source images with diffusion-weighted imaging in patients with acute stroke within 6 hours after onset. Stroke. 2002;33(10):2426–32.
4. Barber PA, Darby DG, Desmond PM, Gerraty RP, Yang Q, Li T, et al. Identification of major ischemic change. Diffusion-weighted imaging versus computed tomography. Stroke. 1999;30(10):2059–65.
5. Fiebach JB, Schellinger PD, Jansen O, Meyer M, Wilde P, Bender J, et al. CT and Diffusion-Weighted MR Imaging in Randomized Order. Stroke. 2002;33(9).
6. 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):1670–4.
7. Phan TG, Donnan GA, Koga M, Mitchell LA, Molan M, Fitt G, et al. The ASPECTS template is weighted in favor of the striatocapsular region. NeuroImage. 2006;31(2):477–81.
8. Pexman JHW, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for Assessing CT Scans in Patients with Acute Stroke. Am J Neuroradiol. 2001:22(8).
9. Schröder J, Thomalla G. A critical review of Alberta stroke program early CT score for evaluation of acute stroke imaging. Front Neurol. 2016;7:245.
10. Bal S, Bhatia R, Menon BK, Shobha N, Puetz V, Dzialowski I, et al. Time dependence of reliability of noncontrast computed tomography in comparison to computed tomography angiography source image in acute ischemic stroke. Int J Stroke. 2015;10(1):55–60.
11. Phan TG, Donnan GA, Koga M, Mitchell LA, Molan M, Fitt G, et al. Assessment of suitability of thrombolysis in middle cerebral artery infarction: a proof of concept study of a stereologically-based technique. Cerebrovasc Dis. 2007;24(4):321–7.

12. Pomerantz SR, Harris GJ, Desai HJ, Lev MH. Computed tomography angiography and computed tomography perfusion in ischemic stroke: a step-by-step approach to image acquisition and three-dimensional postprocessing. Semin Ultrasound CT MR. 2006;27(3):243–70.
13. Boulanger J, Lindsay M, Gubitz G, Smith E, Stotts G, Foley N, et al. Canadian stroke best practice recommendations for acute stroke management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th Edition, Update 2018. Int J Stroke. 2018;13(9):949–84.
14. Forsting M. CTA of the ICA bifurcation and intracranial vessels. Eur Radiol. 2005;15(Suppl 4):D25–7.
15.•• Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723–31 **This is the HERMES group meta-analysis of the five pivotal EVT trials, which provides conclusive evidence of the efficacy of EVT over standard care within 6 hours of symtom onset, in patients selected using NCCT and CTA.**
16. Sylaja PN, Dzialowski I, Puetz V, Eliasziw M, Hill MD, Krol A, et al. Does intravenous rtPA benefit patients in the absence of CT angiographically visible intracranial occlusion? Neurol India. 2009;57(6):739–43.
17. Ajili N, Decroix JP, Preda C, Labreuche J, Lopez D, Bejot Y, et al. Impact of thrombolysis in acute ischaemic stroke without occlusion: an observational comparative study. Eur J Neurol. 2016;23(8):1380–6.
18. Fang X-H, Wang W-H, Zhang X-Q, Liu H-J, Zhang H-M, Qin X-M, et al. Incidence and survival of symptomatic lacunar infarction in a Beijing population: a 6-year prospective study. Eur J Neurol. 2012;19(8):1114–20.
19. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke. 2001;32(12):2735–40.
20. Hoksbergen AW, Fülesdi B, Legemate DA, Csiba L. Collateral configuration of the circle of Willis: transcranial color-coded duplex ultrasonography and comparison with postmortem anatomy. Stroke. 2000;31(6):1346–51.
21. Christoforidis GA, Mohammad Y, Kehagias D, Avutu B, Slivka AP. Angiographic assessment of pial collaterals as a prognostic indicator following intra-arterial thrombolysis for acute ischemic stroke. Am J Neuroradiol. 2005;26(7).
22. Tariq N, Khatri R. Leptomeningeal collaterals in acute ischemic stroke. Journal of vascular and interventional neurology. 2008;1(4):91–5.
23. Liebeskind DS. Collateral circulation. Stroke. 2003;34(9):2279–84.
24. Miteff F, Levi CR, Bateman GA, Spratt N, McElduff P, Parsons MW. The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke. Brain. 2009;132(8):2231–8.
25. Kucinski T, Koch C, Eckert B, Becker V, Krömer H, Heesen C, et al. Collateral circulation is an independent radiological predictor of outcome after thrombolysis in acute ischaemic stroke. Neuroradiology. 2003;45(1):11–8.
26. Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. Ann Neurol. 2007;61(6):533–43.
27. Kim JJ, Fischbein NJ, Lu Y, Pham D, Dillon WP. Regional angiographic grading system for collateral flow. Stroke. 2004;35(6):1340–4.
28. Higashida RT, Furlan AJ. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke. 2003;34(8).
29. Maas MB, Lev MH, Ay H, Singhal AB, Greer DM, Smith WS, et al. Collateral vessels on CT angiography predict outcome in acute ischemic stroke. Stroke. 2009;40(9):3001–5.
30. Lima FO, Furie KL, Silva GS, Lev MH, Camargo ECS, Singhal AB, et al. The pattern of leptomeningeal collaterals on CT angiography is a strong predictor of long-term functional outcome in stroke patients with large vessel intracranial occlusion. Stroke. 2010;41(10):2316–22.
31. Menon BK, Smith EE, Modi J, Patel SK, Bhatia R, Watson TWJ, et al. Regional leptomeningeal score on CT angiography predicts clinical and imaging outcomes in patients with acute anterior circulation occlusions. AJNR. Am J Neuroradiol. 2011;32(9):1640–5.
32. Tan IYL, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, et al. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. AJNR. Am J Neuroradiol. 2009;30(3):525–31.
33. Yeo LLL, Paliwal P, Teoh HL, Seet RC, Chan BP, Ting E, et al. Assessment of intracranial collaterals on CT angiography in anterior circulation acute ischemic stroke. Am J Neuroradiol. 2015;36(2):289–94.
34. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019–30.
35. Menon BK, d'Esterre CD, Qazi EM, Almekhlafi M, Hahn L, Demchuk AM, et al. Multiphase CT angiography: a new tool for the imaging triage of patients with acute ischemic stroke. Radiology. 2015;275(2):510–20.
36. d'Esterre CD, Trivedi A, Pordeli P, Boesen M, Patil S, Hwan Ahn S, et al. Regional comparison of multiphase computed tomographic angiography and computed tomographic perfusion for prediction of tissue fate in ischemic stroke. Stroke. 2017;48(4).
37. Liebeskind DS, Cotsonis GA, Saver JL, Lynn MJ, Cloft HJ, Chimowitz MI, et al. Collateral circulation in symptomatic intracranial atherosclerosis. J Cereb Blood Flow Metab. 2011;31(5):1293–301.
38. Schoellnast H, Tillich M, Deutschmann MJ, Deutschmann HA, Schaffler GJ, Portugaller HR. Aortoiliac enhancement during computed tomography angiography with reduced contrast material dose and saline solution flush. Investig Radiol. 2004;39(1):20–6.
39. Smit EJ, Vonken EJ, van Seeters T, Dankbaar JW, van der Schaaf IC, Kappelle LJ, et al. Timing-invariant imaging of collateral vessels in acute ischemic stroke. Stroke. 2013;44(8):2194–9.
40. Reid M, Famuyide AO, Forkert ND, Sahand Talai A, Evans JW, Sitaram A, et al. Accuracy and reliability of multiphase CTA perfusion for identifying ischemic core. Clinical Neuroradiol. 2018. https://doi.org/10.1007/s00062-018-0717-x. Accessed 7 July 2019.
41. Schregel K, Tsogkas I, Peter C, Zapf A, Behme D, Schnieder M, et al. Outcome prediction using perfusion parameters and collateral scores of multi-phase and single-phase CT angiography in acute stroke: need for one, two, three, or thirty scans? J Stroke. 2018;20(3):362–72.
42. Maier IL, Scalzo F, Leyhe JR, Schregel K, Behme D, Tsogkas I, et al. Validation of collateral scoring on flat-detector multiphase CT angiography in patients with acute ischemic stroke. Meckel S, editor. PLos One. 2018;13(8):e0202592.
43. Wintermark M, Maeder P, Thiran J-P, Schnyder P, Meuli R. Quantitative assessment of regional cerebral blood flows by perfusion CT studies at low injection rates: a critical review of the underlying theoretical models. Eur Radiol. 2001;11(7):1220–30.
44. Wintermark M, Thiran JP, Maeder P, Schnyder P, Meuli R. Simultaneous measurement of regional cerebral blood flow by

perfusion CT and stable xenon CT: a validation study. AJNR. Am J Neuroradiol. 2001;22(5):905–14.
45. Wintermark M, Reichhart M, Cuisenaire O, Maeder P, Thiran J-P, Schnyder P, et al. Comparison of admission perfusion computed tomography and qualitative diffusion- and perfusion-weighted magnetic resonance imaging in acute stroke patients. Stroke. 2002;33(8):2025–31.
46. Wintermark M, Reichhart M, Thiran J-P, Maeder P, Chalaron M, Schnyder P, et al. Prognostic accuracy of cerebral blood flow measurement by perfusion computed tomography, at the time of emergency room admission, in acute stroke patients. Ann Neurol. 2002;51(4):417–32.
47. Parsons MW, Pepper EM, Chan V, Siddique S, Rajaratnam S, Bateman GA, et al. Perfusion computed tomography: prediction of final infarct extent and stroke outcome. Ann Neurol. 2005;58(5):672–9.
48. Eastwood JD, Lev MH, Azhari T, Lee T-Y, Barboriak DP, Delong DM, et al. CT perfusion scanning with deconvolution analysis: pilot study in patients with acute middle cerebral artery stroke. Radiology. 2002;222(1):227–36.
49. Smith WS, Roberts HC, Chuang NA, Ong KC, Lee TJ, Johnston SC, et al. Safety and feasibility of a CT protocol for acute stroke: combined CT, CT angiography, and CT perfusion imaging in 53 consecutive patients. AJNR. Am J Neuroradiol. 2003;24(4):688–90.
50. Kudo K, Terae S, Katoh C, Oka M, Shiga T, Tamaki N, et al. Quantitative cerebral blood flow measurement with dynamic perfusion CT using the vascular-pixel elimination method: comparison with H2(15)O positron emission tomography. AJNR. Am J Neuroradiol. 2003;24(3):419–26.
51. Murphy BD, Fox AJ, Lee DH, Sahlas DJ, Black SE, Hogan MJ, et al. Identification of penumbra and infarct in acute ischemic stroke using computed tomography perfusion–derived blood flow and blood volume measurements. Stroke. 2006;37(7).
52. Nabavi DG, Cenic A, Craen RA, Gelb AW, Bennett JD, Kozak R, et al. CT assessment of cerebral perfusion: experimental validation and initial clinical experience. Radiology. 1999;213(1):141–9.
53. Saini M, Butcher K. Advanced imaging in acute stroke management-part I: computed tomographic. Neurol India. 2009;57(5):541–9.
54. Butcher K, Emery D. Acute stroke imaging. Part II: the ischemic penumbra. The Canadian journal of neurological sciences. J Can Sci Neurol. 2010;37(1):17–27.
55. van der Hoeven EJRJ, Dankbaar JW, Algra A, Vos JA, Niesten JM, van Seeters T, et al. Additional diagnostic value of computed tomography perfusion for detection of acute ischemic stroke in the posterior circulation. Stroke. 2015;46(4):1113–5.
56. Das T, Settecase F, Boulos M, Huynh T, d'Esterre CD, Symons SP, et al. Multimodal CT provides improved performance for lacunar infarct detection. Am J Neuroradiol. 2015;36(6):1069–75.
57. Campbell BCV, Weir L, Desmond PM, Tu HTH, Hand PJ, Yan B, et al. CT perfusion improves diagnostic accuracy and confidence in acute ischaemic stroke. J Neurol Neurosurg Psychiatry. 2013;84(6):613–8.
58. Rudilosso S, Urra X, San Román L, Laredo C, López-Rueda A, Amaro S, et al. Perfusion deficits and mismatch in patients with acute lacunar infarcts studied with whole-brain CT perfusion. AJNR. Am J Neuroradiol. 2015;36(8):1407–12.
59. Butcher K, Parsons M, Allport L, Lee SB, Barber PA, Tress B, et al. Rapid assessment of perfusion-diffusion mismatch. Stroke. 2008;39(1):75–81.
60. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med. 2012;366(12).
61. Kate M, Wannamaker R, Kamble H, Riaz P, Gioia LC, Buck B, et al. Penumbral imaging-based thrombolysis with Tenecteplase is feasible up to 24 hours after symptom onset. J Stroke. 2018;20(1):122–30.
62. Butcher K, Parsons M, Baird T, Barber A, Donnan G, Desmond P, et al. Perfusion thresholds in acute stroke thrombolysis. Stroke. 2003;34(9):2159–64.
63. Ma H, Parsons MW, Christensen S, Campbell BCV, Churilov L, Connelly A, et al. A multicentre, randomized, double-blinded, placebo-controlled phase III study to investigate extending the time for thrombolysis in emergency neurological deficits (EXTEND). Int J Stroke. 2012;7(1):74–80.
64. Lansberg MG, Lee J, Christensen S, Straka M, De Silva DA, Mlynash M, et al. RAPID automated patient selection for reperfusion therapy. Stroke. 2011;42(6):1608–14.
65. Bivard A, Levi C, Lin L, Cheng X, Aviv R, Spratt NJ, et al. Validating a predictive model of acute advanced imaging biomarkers in ischemic stroke. Stroke. 2017;48(3):645–50.
66.• Wannamaker R, Guinand T, Menon BK, Demchuk A, Goyal M, Frei D, et al. Computed tomographic perfusion predicts poor outcomes in a randomized trial of endovascular therapy. Stroke. 2018;49(6):1426–33 **This retrospective analysis of patients who were evaluated with multimodal CT, including CTP, in the ESCAPE trial, indicated that patients with non-penumbral patterns had worse outcomes, irrespective of treatment.**
67. Austein F, Riedel C, Kerby T, Meyne J, Binder A, Lindner T, et al. Comparison of perfusion CT software to predict the final infarct volume after thrombectomy. Stroke. 2016;47(9):2311–7.
68. Yu Y, Han Q, Ding X, Chen Q, Ye K, Zhang S, et al. Defining core and penumbra in ischemic stroke: a voxel- and volume-based analysis of whole brain CT perfusion. Sci Rep. 2016;6:20932.
69. Lima FO, Lev MH, Levy RA, Silva GS, Ebril M, De Camargo ÉC, et al. Functional contrast-enhanced CT for evaluation of acute ischemic stroke does not increase the risk of contrast-induced nephropathy. Am J Neuroradiol. 2010;31(5):817–21.
70. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018;49(3):e46–110.
71. Davis SM, Donnan GA, Butcher KS, Parsons M. Selection of thrombolytic therapy beyond 3 h using magnetic resonance imaging. Curr Opin Neurol. 2005;18(1):47–52.
72. Group TNI of ND and S rt-PSS. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333(24):1581–8.
73. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. JAMA. 1995;274(13):1017.
74. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet. 1998;352(9136):1245–51.
75. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT investigators. Prolyse in acute cerebral thromboembolism. Stroke. 1998;29(1):4–11.
76. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS study: a randomized controlled trial. Alteplase thrombolysis for acute noninterventional therapy in ischemic stroke. JAMA. 1999;282(21):2019–26.

77. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in acute cerebral thromboembolism. JAMA. 1999;282(21):2003–11.
78. Ogawa A, Mori E, Minematsu K, Taki W, Takahashi A, Nemoto S, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke. Stroke. 2007;38(10):2633–9.
79. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with Alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359(13):1317–29.
80. IST−3 collaborative group TI-3 collaborative, Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet. 2012;379(9834):2352–63.
81. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med. 2013;368(10):893–903.
82. Huang X, Cheripelli BK, Lloyd SM, Kalladka D, Moreton FC, Siddiqui A, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. Lancet Neurol. 2015;14(4):368–76.
83. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of Intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11–20.
84. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372(24):2296–306.
85. Campbell BCV, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11).
86. Saver JL, Goyal M, Bonafe A, Diener H-C, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285–95.
87. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol. 2016;15(11):1138–47.
88. Mocco J, Zaidat OO, von Kummer R, Yoo AJ, Gupta R, Lopes D, et al. Aspiration thrombectomy after intravenous Alteplase versus intravenous Alteplase alone. Stroke. 2016;47(9):2331–8.
89. Muir KW, Ford GA, Messow C-M, Ford I, Murray A, Clifton A, et al. Endovascular therapy for acute ischaemic stroke: the pragmatic Ischaemic stroke thrombectomy evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry. 2017;88(1):38–44.
90. Logallo N, Novotny V, Assmus J, Kvistad CE, Alteheld L, Rønning OM, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurol. 2017;16(10):781–8.
91. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, et al. Tenecteplase versus Alteplase before thrombectomy for ischemic stroke. N Engl J Med. 2018;378(17):1573–82.
92.•• Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med. 2018;378(8):708–18 **The DEFUSE 3 trial demonstrated that multimodal CT, including objective CTP assessment, can be used to select patients who benefit from EVT in the 'late window' (>6 hours and up to 16 hours after onset). These results, along with those of reference 72 led to guideline and practice change.**
93.•• Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. New England Journal of Medicine. 2018;378(1):11–21 **The DAWN trial demonstrated that multimodal CT, including objective CTP assessment, can be used to select patients who benefit from EVT in the 'late window' (>6 hours and up to 24 hours after onset). These results, along with those of reference 77 led to guideline and practice change.**
94.•• Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. N Engl J Med. 2019;380(19):1795–803 **The EXTEND trial demonstrated that multimodal CT, including objective CTP assessment, can be used to select patients who benefit from intravenous thrombolysis with alteplase up to 9 hours after onset.**
95. Campbell BCV, Majoie CBLM, Albers GW, Menon BK, Yassi N, Sharma G, et al. Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. The Lancet Neurology. 2019;18(1):46–55.
96. Ringleb P, Bendszus M, Bluhmki E, Donnan G, Eschenfelder C, Fatar M, et al. Extending the time window for intravenous thrombolysis in acute ischemic stroke using magnetic resonance imaging-based patient selection. Int J Stroke. 2019. https://doi.org/10.1177/1747493019840938. Accessed 7 July 2019.
97. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar imaging thrombolytic evaluation trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol. 2008;7(4):299–309.
98.•• Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendszus M, et al. Extending thrombolysis to 4·5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. Lancet. 2019; **This meta-analysis of the EXTEND, ECASS 4-EXTEND, and EPITHET trials confirmed that multimodal penumbral assessment can be used to select patients who benefit from intravenous thrombolysis with alteplase up to 9 hours after onset.**
99. Smith C, Al-Nuaimi Y, Wainwright J, Sherrington C, Singh A, Kallingal J, et al. The influence of bolus to infusion delays on plasma tissue plasminogen activator levels. Int J Stroke. 2014;9(7):939–42.
100. Hill MD, Goyal M, Demchuk AM, Fisher M. Ischemic stroke tissue-window in the new era of endovascular treatment. Stroke. 2015;46(8):2332–4.
101. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, et al. European stroke organisation (ESO)—European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical Thrombectomy in acute Ischaemic StrokeEndorsed by stroke Alliance for Europe (SAFE). Eur Stroke J. 2019;4(1):6–12.
102. Clinical Guidelines for Stroke Management. Stroke Foundation of Australia Stroke. 2017. https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management-2017. Accessed 16 July 2019.