Local Coverage Determination (LCD): Computed Tomography Cerebral Perfusion Analysis (CTP) (L38709)

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Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

CTP (using automated post-processing software algorithmic analysis) is medically reasonable and necessary in patients with acute ischemic stroke (AIS) caused by unilateral large vessel occlusion (LVO) in the proximal anterior circulation evaluated at stroke centers; CTP can be used to aid in selection for endovascular mechanical thrombectomy (EVT) if one of the following other conditions is fulfilled:

1. Treatment (femoral puncture) can be started within **6-24 hours** of the time last known to be at neurologic baseline and who meet the pre-CTP inclusion/exclusion criteria as defined by the DAWN trial[1], or
2. Treatment (femoral puncture) can be started within **6-16 hours** of the time last known to be at neurologic baseline and who meet the pre-CTP inclusion/exclusion criteria as defined by the DEFUSE 3 trial[2]

*excluding criteria purely related to study mechanics (e.g., able to return for protocol required follow-up visits, etc.)

Table 1: Key Inclusion Criteria for DAWN and DIFUSE 3

Parameter	DAWN	DEFUSE 3
Prestroke baseline mRS (0-6)	mRS ≤1 (no significant disability)	mRS ≤2 (slight disability)
Last known well to treatment time	6-24 h	6-16 h
Minimum NIHSS score (0-42)	10 (moderate stroke)	6 (moderate stroke)
LVO by MR or CT angiography	ICA (intracranial) and/or M1 segment of MCA	ICA (cervical or intracranial) and/or M1 segment of MCA

mRS= modified Rankin scale, NIHSS= National Institutes of Health Stroke Scale, ICA= internal carotid artery, MCA= middle cerebral artery

Background

Stroke is the leading cause of adult disability in the United States with limited treatment options [3]. The FDA approved treatment for stroke is intravenous tissue plasminogen activator (tPA) within three hours after onset of symptoms. Often treatment is not initiated since most patients do not present within this narrow time window, resulting in only 4% of patients receiving tPA treatment. Even with treatment, only 12-25% benefit as irreversible injury may have already occurred, or the treatment fails to recanalize the occluded artery with reported recanalization rate of 10-50% [2,4]. Endovascular stroke therapy involves mechanical removal of blood clots or intra-arterial administration of thrombolytics. This offers an alternative to patients who fail tPA or are not eligible. Recanalization rates are as high as 82% for thrombectomy[5]. Initial studies on EVT failed to demonstrate clinical benefits[2]. Further investigation suggested the lack of benefit was related to patient selection. Subsequent studies identified imaging criteria to determine patients with potentially salvageable tissues and improved outcomes from EVT[6-8]. In stroke victims, there is the ischemic penumbra, potentially salvageable tissue, and ischemic core, which is irreversibly injured. Patients with >50% reperfusion have been shown to have an improved outcome compared to those with <50% reperfusion. Treatment of patients with a higher likelihood of improved outcomes demonstrates the benefit of EVT in select patients. Expansion of the treatment window up to 16-24 hours has promising results in appropriately selected patients expanding the possibility for acute stroke treatment[2,9]. CPT plays a role as it can be used to calculate the ischemic penumbra and help to identify which patients may benefit from EVT. Reperfusion treatment was found to be more common in patients who had imaging with CTA (13%) or CTP (17.6%)[10].

Noncontrast CT (NCCT) is the mainstay for initial AIS imaging due to widespread availability, rapid scan times, and detection of intracranial hemorrhage (which leads to very different management from infarction). Multimodal CT includes NCCT, CT angiography (CTA) (to assess the site of vascular occlusion), and CT Perfusion Imaging (CTP). CTP is typically performed after NCCT and consists of a temporal sequence of head CT scans obtained during the wash-in and wash-out of an IV bolus of iodinated contrast agent. Post-acquisition data analysis by dedicated software allows the creation of multiple hemodynamic parametric maps (based on contrast time-density curves) for clinical interpretation. Hemodynamic parameters include time to maximum contrast intensity (Tmax), mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV), mathematically related by the equation CBF = CBV/MTT [11]. The CBV is calculated as the milliliters of blood per 100g of brain tissue. These maps can estimate brain regions with a high probability of irreversible infarction (ischemic core) versus areas of potentially reversible ischemia (penumbra). Both core and penumbra are estimates of probabilistic tissue fate. Penumbra imaging has been proposed as a useful predictor of hemorrhagic transformation (HT) in AIS [12]. HT occurs in up to 40% of stroke patients and is related to rapid deterioration and poor outcomes. CTP has been studied in acute ischemic stroke for decades [13], only recently was it found likely to influence treatment decision [14]. Subsequently, two level I randomized controlled trials (RCTs) (DAWN and DEFUSE 3) found CTP helped determine eligibility for EVT in the late time period (6-24 hr.) of an acute (<24 hr.) ischemic stroke (AIS) [2,9], a paradigm shift away from confinement to the early window (< 6 hr.).

CTP has the advantage of being able to be performed by most multi-slice scanners and add minimal time, usually less than 10 minutes, to the evaluation. There are limitations to CPT technology, emphasizing that CTP must be performed in properly selected patients. There are potential technical issues such as patient movement and poor contrast bolus that can impact results. While experienced providers can typically recognize abnormalities caused by artifacts, calculations provided by the software may include artifacts, risking overestimating the penumbral volume. This requires manual correction to avoid miscalculations. Another challenge is there are multiple CTP vendor software and postprocessing techniques, which may lead to variations in calculated core and mismatch [11,15]. Ideally, the software programs would be standardized, but given the variability, providers must be familiar with the software package being used and potential variations in calculated values. Automation has the potential to reduce human variability; however, even with fully automated software, a significant clinician interpretation learning curve remains [16]. Limitations of arterial flow, which can be caused by low cardiac output, arrhythmias, chronic carotid stenosis,

may result in overestimations. Chronic infarction, vascular stenosis, chronic white matter changes, seizures, and vasospasm can demonstrate abnormal CTP patterns and potentially mimic acute ischemia, so the provider must consider the full medical picture when interpreting results [11,17]. CTP requires contrast, so those with renal failure or known serious allergy to iodine and previously refractory to pretreatment medications may not be candidates. Protocols should include care to avoid excess radiation exposure and avoid treatment delays.

Summary of Evidence

CTP for AIS

CTP in acute stroke management: A 2020 systematic review aimed to evaluate the diagnostic accuracy of CTP in the prediction of hemorrhagic transformation and patient outcome in AIS reported CTP sensitivity as 85.9%, a specificity of 73.9%, positive predictive value 60.3% and negative predictive value of 92.9% [12]. A 2017 systematic review identified 27 studies with a total of 2168 patients. The pooled sensitivity of CTP for acute ischemic stroke was 82% (95% CI 75–88%), and the specificity was 96% (95% CI 89–99%). They determined CTP was more sensitive than NCCT and had a similar accuracy with CTA, but also that the evidence was not strong, and there is a need for high-quality evidence to confirm results [18]. Older systematic reviews report mixed results with a wide range in sensitivity and specificity of CTP for the detection of AIS [18]. A 2019 systematic review and meta-analysis comparing imaging modalities for evaluation of AIS concludes that while CTP was more accurate than NCCT for detection of AIS, it was less accurate than diffusion-weighted imaging (DWI) MRI (sensitivity 82%, specificity 96% vs. sensitivity 15-86%, specificity 100%, respectively) [19].

A 2020 systematic review reported prediction of the HT could guide decision making in regards to consideration at thrombolysis decision point and concludes CTP is a useful prognostic tool for clinicians at the point of intervention decision making for AIS [12]. This review, however, consisting of three prospective and nine retrospective studies, is subject to inaccuracy given the risk of bias and a high degree of heterogenicity in the selected studies. On the contrary, a large prospective trial with 545 patients treated with IV tPA or thrombectomy had CTP at admission, and day three follow-up looked at the ability of the technology to predict HT (by measurement of the blood-brain barrier permeability (BBBP). While univariate analysis associated BBBP measured by CTP as an independent predictor of HT, the multivariant analysis did not reproduce those findings, and the addition of BBBP as a variable did not change the AUC (0.77, 95% CI 0.71–0.83) of the model. The authors concluded BBBP measured by CTP did not improve prediction of HT, and improvements are needed before being considered "a useful addition to decision making" [20].

Most studies evaluating the role of CTP in AIS are retrospective with variability in inclusion and exclusion criteria, outcomes reported, and sampling procedures, which introduces a high risk for bias, heterogenicity, and overall reduced quality of evidence. The evidence for routine use of CTP for evaluation for AIS is low quality, and there is a need for high-quality evidence to determine the role it may play in AIS evaluation. The exception is the role of CTP for evaluation for patient selection for EVT.

There are two level I randomized controlled trials (RCTs), which both conclude CTP is useful in determining eligibility for EVT in the late time period (6-24 hr.) of an acute (<24 hr.) ischemic stroke (AIS). The DAWN trial (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) studied whether patients with a clinical deficit that is disproportionately severe relative to the infarct volume may benefit from late EVT[9]. See the table for key inclusion criteria. All patients had evidence of occlusion in ICA with CT or MRI imaging with CTP or DWI to determine infarct volume, and the cut-off values for clinical-core mismatch varied based on age, and NIHSS score ranging from 20-50mL. Patients were randomly assigned to EVT plus standard medical management (MM) (N=107, mean age 69.4 yr.) or to MM alone (N=99, mean

age 70.7 yr.). Median National Institutes of Health Stroke Scale (NIHSS) score was 17 (moderate to severe stroke) for both groups. The trial was stopped for efficacy at the first interim analysis. At 90 days, the rate of functional independence, as defined by a score of 0-2 on the modified Rankin scale (mRS) of 0-6, was greater for EVT than MM (49% versus 13%; adjusted difference, 33%; 95% CI, 21–44; posterior probability of superiority >0.999). The rate of symptomatic intracranial hemorrhage did not differ significantly between the two groups (6% in the EVT group and 3% in the MM group, P=0.50), nor did 90-day mortality (19% and 18%, respectively; P=1.00).

The DEFUSE 3 trial (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) was a multicenter, randomized, open-label trial randomizing patient with occlusion in the ICA or MCA based on CTA or MRA (Table 1). In patients with NIHSS ≥6, (1) penumbra volume ≥15 ml, (2) penumbra to core ratio ≥1.8, and (3) core volume ≤70 ml were used as imaging eligibility criteria to select patients for late EVT (where penumbra volume is the perfusion-core mismatch which is defined as the Tmax>6s volume minus core volume, and the core volume is measured by CTP or MRI diffusion). See the table for key inclusion criteria. Patients were randomly assigned to EVT plus standard MM or standard MM alone. The trial was conducted at 38 U.S. centers and terminated early for efficacy after 182 patients had undergone randomization (EVT N=92, median age 70; MM N=90, median age 71). The median NIHSS score was 16 (moderate to severe stroke) for both groups. The EVT group showed a benefit in functional outcome at 90 days (mRS score 0–2, 44.6% versus 16.7%; RR, 2.67; 95% CI, 1.60–4.48; P<0.0001). The 90-day mortality rate trended in favor of EVT (14% vs. 26% (P=0.05)), and there was no significant difference between groups in the rate of symptomatic intracranial hemorrhage (7% and 4%) or serious adverse events (43% and 53%). In a subgroup analysis, both the favorable outcome rate and treatment effect did not decline in transfer patients compared to direct-admission patients [22].

The DAWN and DEFUSE 3 trials differed in their approach in identifying salvageable brain (table). The DAWN trial selected patients based on a clinical-core mismatch, whereas the DEFUSE 3 trial focused on a penumbra-core mismatch. Both target the same conceptual goal, identifying patients with enough salvageable, at risk, tissue to warrant EVT. In both cases, brain tissue was designated as having irreversible injury if CBF was less than 30% of that seen in contralateral perfused tissue by CTP (or less commonly, magnetic resonance MR (MR) perfusion-weighted imaging (MR-PWI)) as detected by RAPID automated perfusion post-processing software. Both trials demonstrated a large clinical benefit, with numbers needed to treat (NNT) of 3-4 to prevent functional dependence. There were differences in the protocols as well. Dawn excluded patients with an infarct involving more than one-third of the territory of the MCA at baseline. DEFUSE-3 enrolled patients with lower NIHSS score (less clinical severity), larger core infarct, and slightly higher baseline mRS disability score. One-third of DAWN-eligible patients are DEFUSE-3 ineligible. Epidemiologic data suggest that about one-third of AIS patients present between 6-24 hours, and only 9.2% of these (or 2.7% overall) meet DAWN or DIFFUSE 3 inclusion criteria [23,24]. Of all patients with acute ischemic stroke presenting to a single comprehensive stroke center, 1.7% of patients qualified for DAWN clinical trial enrollment with an additional 0.6-1% qualifying for the DEFUSE-3 trial [23].

Both studies employed CTP or MR-PWI to select patients for EVT, with CTP predominating. DEFUSE 3 subgroup analysis showed no statistical difference in treatment effect between "patients selected on the basis of diffusion/perfusion MRI and those selected on the basis of CT perfusion imaging," however, the authors admit statistical power was limited by the lower number of patients enrolled as a result of early termination. DAWN subgroup analysis did not include comparison by qualifying image method. One criticism of both studies was the large number of "wake-up strokes" (50%) vs. 14-28% in the general population, perhaps contributing to overestimation of stroke age, and therefore, better outcomes[25,26]. The authors note that a higher proportion of unwitnessed strokes are expected in trials enrolling patients late after onset, as witnessed strokes are typically treated early, and that the benefit persisted even after stratification into witnessed and unwitnessed stroke groups [27,28]. They also explain that outcomes were "paradoxically" superior to early window (< 6 hr.) treatment trials, probably due to selection for a large volume of penumbral (i.e., salvageable) tissue.

A subsequent prospective review [29] and retrospective registry [30] analysis also support the value of CTP in late period EVT eligibility assessment, while also emphasizing the need to correlate perfusion abnormalities with other

imaging (NCCT, CTA) and clinical information; they may be more sensitive than CTP for detecting irreversibly damaged tissue as time progresses. While DWI is considered the gold standard, CTP has the advantage of more availability, faster acquisition, and a similar estimate of mismatch, therefore becoming the dominant advanced imaging tool for identifying the core and penumbra [31]. Results, however, must still be interpreted with caution. A 2020 retrospective study that evaluated patients undergoing CTP for EVT triage included 176 consecutive patients undergoing CTP and CTA. Automated calculations were performed with proprietary software, and failures were reprocessed manually. The primary outcome was postprocessing failure, defined as the presence of perfusion abnormalities caused by artifact and verified on follow-up images, and was reported in 11% of cases (20/176). Causes included severe motion, streak artifact, and poor arrival of contrast. Half of the failures (n=6) led to erroneous ischemic core volumes that may have resulted in different treatment decisions if the CTP results had not been corrected. The authors conclude that results from automated CPT should be interpreted with caution, and failures should be recognized and corrected to ensure appropriate management decisions are made[32]. In most cases, the key to improved diagnostic certainty is to interpret the CTP, not in isolation, but in conjunction with the NCCT, CTA, NIHSS, and clinical history [31].

Non-AIS indications

CTP for cerebral ischemia due to subarachnoid hemorrhage (SAH): One non-ischemic stroke CTP potential use is in determining delayed cerebral ischemia (DCI), occurring in approximately 30% of patients within two weeks after aneurysmal SAH[33]. The most common etiology of DCI is thought to be vasospasm produced by spasmogenic substances generated during lysis of subarachnoid blood. Monitoring for DCI can be done with CTA to confirm vasospasm in patients with elevated velocities on transcranial Doppler (TCD) ultrasound [33]. However, brain perfusion asymmetry on CTP has been studied for this purpose as well. A 2014 systematic review and meta-analysis [34], included four small observational studies of 188 patients[35-38]. The weighted averages and ranges of the pooled sensitivity and specificity of CTP in the determination of DCI were 0.84 (0.7-0.95) and 0.77 (0.66-0.82), respectively. The pooled odds ratio was 23.14 (95% CI, 5.87-91.19). The authors conclude that "perfusion deficits on CTP "may be helpful in identifying patients with delayed DCI before the development of infarction and neurologic deficits." However, they also cite many definitional and methodology limitations of the underlying studies (nonuniform DCI definition as an outcome measure, CTP protocol and postprocessing software differences, lack of consistency of what constitutes an abnormal CTP test result, the optimal time to perform CTP, and nonstandard hemodynamic parameter thresholds). In addition, accurate quantification is dependent on an intact blood-brain barrier, which may not be functioning in DCI.

CTP for Traumatic Brain Injury: Small cohort studies have explored the potential role of CTP for patients with traumatic brain injury (TBI). A small study of 48 patients reported NCCT had a sensitivity of 39.6% compared to improved sensitivity of CTP of 87.5% for cerebral contusions diagnosed on delayed follow-up imaging [39]. Additional studies suggest reductions in blood flow and volumes determined by CTP are associated with worse outcomes[40] . A subset analysis of 30 patients from an observational study reported the information obtained from CTP is useful in decision making [41].

CTP for neoplasia: CTP has been proposed as a possible modality for non-invasive assessment of brain tumors. Several small (<20 patients) retrospective reports evaluated CTP to distinguish malignant verses normal tissue, evaluation for metastatic disease, and differentiating tissue type in brain tumors report promising early results [42,43]. A small prospective trial of 49 consecutive patients with brain tumors or tumor-like lesions were evaluated with CT and CTP. The results suggest CTP can aid in distinguishing glioma and lymphomas based on quantitative measurements of cerebral blood volume (CBV) and permeability [44]. The reports indicate the need for further investigation of cut-off values, accuracy, and patient selection criteria to determine if clinically useful. A meta-analysis of 13 prospective studies totaling 389 patients with head and neck tumors demonstrated feasibility for routine clinical use of CTP, but reported small size of the patient population, heterogeneity of the patient population, considering different end points of outcome and enrolling HNC in various stages limited the results and results would

need to be validated [45].

Analysis of Evidence
(Rationale for Determination)

The 2019 update to the 2018 American Heart Association (AHA)/American Stroke Association (ASA) guidelines [46] for the early management of patients with AIS state "In selected patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP, DW-MRI, with or without MRI perfusion is recommended to aid in patient selection for mechanical thrombectomy, but only when imaging and other eligibility criteria from RCTs showing benefit are being strictly applied in selecting patients for mechanical thrombectomy". (Class of recommendation I-strong; level (quality) of evidence A) [47]. Since only the DAWN and DEFUSE 3 RCTs show a benefit of late-period EVT, they further warn: "DAWN or DEFUSE 3 eligibility should be strictly adhered to in clinical practice." These guidelines do not recommend CTP to determine eligibility for either thrombolytic therapy or EVT in the early (<6 hours) period (Class of recommendation I-strong; level (quality) of evidence B-Nonrandomized), or for any other indication (e.g., prediction of hemorrhagic transformation in acute ischemic injury). Other guidelines have similar recommendations [48-50].

National Institute for Health and Care Excellence recommends: "If thrombectomy might be indicated, perform imaging with CT contrast angiography following initial non-enhanced CT. Add CT perfusion imaging (or MR equivalent) if thrombectomy might be indicated beyond 6 hours of symptom onset.[51]" This recommendation uniquely also includes posterior circulation stroke. However, there is minimal evidence regarding the appropriate threshold and utility of CTP in the posterior circulation, and MRI is a better alternative[11] .

ECRI Clinical Evidence Assessment on Perfusion CTP reviewed the literature on CTP as an alternative imaging evaluation in addition to NCCT. It determined the evidence was "inconclusive" due to mixed results. They report "CTP's clinical utility compared with that of NCCT and magnetic resonance imaging (MRI) for assessing AIS has not been established because of too few data. No studies compared CTP clinical utility with other imaging methods. The RCT focused on treatment and did not randomly assign imaging methods, which created a risk of selection bias when comparing CTP to perfusion MRI. Most studies assessed in the SRs, as well as the diagnostic accuracy studies published after the SRs, were at high risk of bias due to retrospective design and single-center focus [52].

The 2017 American College of Radiology (ACR)-American Society of Neuroradiology (ASNR)-Society of Pediatric Radiology (SPR) guidelines lists primary and secondary indications for CTP in neuroradiology, including evaluation of AIS, neoplasia, trauma, cerebral hemorrhage, and vasospasm following subarachnoid hemorrhage [53]. The 2017 ACR Appropriateness Criteria Cerebrovascular Disease grades CTP at the level of "may be appropriate" and report that "CTP can be used to evaluate cerebrovascular reserve; however, its role in the evaluation of acute stroke remains unproven." They also state, "CTP may play a role to evaluate for ischemia when MRI is contraindicated or cannot be performed". Additionally, CTP has shown some promise in identifying patients who may benefit from therapy outside the accepted treatment window"[54].

The 2012 AHA/ASA guidelines for the management of aneurysmal SAH state that "perfusion imaging with CT or magnetic resonance can be useful to identify regions of potential brain ischemia" (Class Ia; Level of Evidence B) [55]. However, current UpToDate guidance concludes that CTP "clinical utility...remains to be established" and that "the use of this technique as a monitoring tool may be limited by risks of recurrent dye loads and radiation exposure" [56], as well as by lack of standardized methodology [34]. The 2015 AHA/ASA guidelines for the management of spontaneous intracerebral hemorrhage has no mention of CTP [57], nor does UpToDate [58]. Regarding trauma and oncologic indications, there appears to be insufficient evidence to support the routine use of CTP.

In summary, we consider the concordant level I evidence of a large clinical benefit after CTP imaging (using automated post-processing software algorithmic analysis) in AIS secondary to LVO, to assist in late EVT eligibility determination per AHA/ASA guidelines, medically reasonable and necessary. Other stroke or non-stroke indications lack level I evidence and are not considered medically reasonable and necessary at this time.

General Information

Associated Information

N/A

Sources of Information

N/A

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Revision History Information

N/A

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)
A58223 - Billing and Coding: Computed Tomography Cerebral Perfusion Analysis (CTP)
A58520 - Response to Comments: Computed Tomography Cerebral Perfusion Analysis (CTP)

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