Current advances in CT imaging of stroke

Stroke, brain attack, ischemic event and infarction are all terms used to describe the second most common cause of death in the USA in people over the age of 60. Imaging plays a pivotal role not only in stroke detection, but also in predicting infarct extent, hemorrhagic risk, tissue fate and clinical outcome. Noncontrast CT remains the modality of choice for investigation of acute stroke, with the use of the Alberta Stroke Program Early CT Score, CT angiography source images and CT perfusion significantly improving sensitivity. Hemorrhagic conversion risk may be predicted using permeability surface area product maps. The CT angiographic spot sign and postcontrast leakage visible on contrast CT can predict hematoma expansion in primary intracerebral hemorrhage. Clot burden and collateral blood-supply assessment can help identify patients who may benefit the most from more aggressive thrombolytic techniques. Physiological imaging of the ischemic penumbra may help identify selected patients that would benefit from thrombolysis beyond the current 4.5 h treatment window.

**KEYWORDS:** clot burden | CT angiography | CT angiography spot sign | CT perfusion | hemorrhagic conversion | penumbra | recombinant tissue plasminogen activator | stroke

*Stroke Program Early CT Score (ASPECTS)*

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sensitivity by increasing the distinction between gray- and white-matter density. Knowledge of infarction side does not appear to improve detection [18–20], whereas level of experience does [21]. NC-CT therefore may be negative in 40–60% of cases within 3 h of symptom onset.

The addition of CT angiography (CTA) provides valuable information relating to vessel occlusion and degree of collateralization; furthermore, it has also been shown to improve infarct detection [22–24]. By using CTA-source images (SI) reconstructed into 3-mm slices, the sensitivity and specificity of MCA infarct detection, excluding small lacunar lesions, is 75–95% and 80–90%, respectively [25].

Visually, the contrast afforded by CTA-SI may visualize alterations in blood volume, which may not yet be associated with a threshold sufficient to result in NC-CT changes. The infarct detected on CTA-SI correlates well with the diffusion-weighted MRI abnormality and is an independent predictor of final infarct volume size in patients presenting within 6 h [23]. Applying ASPECTS scoring method to CTA-SI data and using a threshold of 7 or less has been demonstrated to be more sensitive than NC-CT [25] for final infarct prediction. Using this CTA-SI ASPECTS threshold may result in fewer patients being misclassified into groups that may result in inappropriate treatment compared with NC-CT.

Computed tomography perfusion (CTP) data add the ability to differentiate between the infarct core and the ischemic penumbra. However, CTP data also have the ability to improve infarct detection [28–32]. The accuracy of CTP for stroke detection and extent determination is 72–86%. Sensitivities and specificities lie between 78 and 95%, respectively (Figure 1). False negatives are usually due to inadequate spacial coverage, lacunar infarcts or failure to detect multiple small emboli [33].

Computed tomography perfusion ASPECTS scoring (applying the same criteria as NC-CT ASPECTS but on CTP data) has been shown to be predictive of clinical outcome. Specifically, using cerebral blood volume (CBV) data and utilizing an ASPECTS threshold of 8 has been shown to predict patients who experience major neurologic improvement and have good clinical outcomes at 3 months (modified Rankin scale ≤2) [25,34]. Another study also reported a benefit of CBV ASPECTS over NC-CT [35]. However, a lower threshold of 6–7 was used resulting in a higher false-negative rate of 13–18%.

**Advances in extending the treatment time window**

Thrombolytic therapy utilizing rtPA is currently the only approved medical therapy for the treatment of acute stroke if initiated within 4.5 h [36]. The NINDS study group was the first to report a significant benefit in patients who received rtPA, where patients were 30% more likely to have minimal or no disability at 3 months than were patients who received placebo [15]. However, the benefit of thrombolytic therapy is clearly time dependent, and may not end at the current 3–4.5 h time limit. Further evaluation of the NINDS data [37], as well as a large meta-analysis of several large stroke studies [15,39–42], confirm that the benefit of thrombolytic therapy decreases with time from the onset of symptoms. However, both studies reported that this benefit likely extends beyond 3 h, but not likely to 6 h. In most countries, currently fewer than 2% of patient's are treated with rtPA for acute stroke, primarily owing to delayed presentation to a stroke center [43].

Several earlier studies have investigated a treatment time window of 0–6 h after the onset of symptoms; however, these have failed to show a significant advantage with thrombolytic therapy beyond 3 h [39–41,44]. The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) also looked at thrombolytic therapy 3–6 h after onset of symptoms and showed a trend towards lower infarct growth for patients receiving rtPA, but failed to show significance owing to small numbers [45]. Nevertheless, this study did show a significant association between reperfusion and improved clinical outcomes, suggesting reperfusion as a surrogate for clinical outcome.

The ECASS III investigators are the first to demonstrate a significant benefit from thrombolysis beyond 3 h and up to 4.5 h [36]. With a larger number of patients enrolled, an absolute benefit over the placebo group of 7.2% was demonstrated up to 4.5 h after treatment onset. A significantly higher incidence of symptomatic hemorrhage was demonstrated in the rtPA group;
however, this was still quite rare (2.4%), with the incidence similar to other studies using a 3 h time window [15,40,46]. There was, however, no significant difference in mortality when the treatment window was extended to 4.5 h. Previously reported odds ratios for predicting a good clinical outcome following thrombolytic therapy clearly decrease with time, with an odds ratio of 2.81 for treatment within 0–90 min following symptom onset and falling to 1.55 for treatment 91–180 min following symptom onset [38]. The ECASS III investigators reported an odds ratio of 1.34 for patients treated 181–270 min following symptom onset. Although it now appears that thrombolytic therapy is beneficial in the unselected patient up to 4.5 h following symptom onset, patients should still be treated as soon as possible to gain the greatest benefit.

Physiological selection of patients may enable extension of the treatment time window. This approach would allow a selection of ideal patients within the traditional 4.5 h window but also include patients beyond conventional treatment time windows to be considered for treatment. The desmoteplase in acute stroke studies eloquently demonstrated this principle utilizing a visually determined 120% diffusion-weighted MRI/perfusion-weighted MRI mismatch for patient enrollment up to 9 h. The use of a more fibrin-specific thrombolytic in

Figure 1. Additional benefit of CT perfusion to detect infarct not discernible on noncontrast CT and CT angiography source images. (A) Noncontrast CT demonstrates hypodensity and loss of gray–white matter differentiation in right frontal operculum (*). Findings are consistent with remote infarct. (B) CT angiography source images confirms right frontal abnormality. No other infarct is seen. (C) Cerebral blood flow, (D) cerebral blood volume and (E) mean transit time CT perfusion maps confirm right frontal opercular lesion, but demonstrates a second lesion in posterior left temporal lobe (arrowheads) with minor associated cerebral blood volume abnormality consistent with infarct and (F) diffusion-weighted image confirms left sided infarct (arrow).
this extended time period was associated with symptomatic hemorrhage rates comparable with studies shorter than 4.5 h. Despite a promising clinical efficacy in the Phase II studies [47,48], a subsequent Phase III study failed to show clinical benefit due to a variety of factors, including enrollment of patients without vessel occlusion, low placebo baseline National Institutes of Health Stroke Scale (NIHSS) scores and nondrug related, nonhemorrhagic deaths in the treatment group [49]. A number of questions remain to be answered before physiological imaging becomes a reality. There is some doubt in neurology circles as to how many patients may still demonstrate a penumbra in the extended time window. Anecdotally and experimentally, the ischemic penumbra is also demonstrated to decrease progressively with time from symptom onset, but is also shown to persist in up to 44% of patients imaged 18–24 h following symptom onset [50]. There is much optimism that appropriately selected subsets of acute stroke patients with persisting penumbra and a vessel occlusion may benefit from thrombolytic therapy well beyond the 4.5 h time window.

**Advances in predicting hemorrhagic transformation of infarct risk & intracerebral hemorrhage expansion**

An important function of NC-CT is the detection of intracranial hemorrhage — a contraindication to thrombolysis. However, hemorrhagic transformation is seen in up to 43% of CT studies [15,40,47,51]. Hemorrhagic transformation is considered a complication of thrombolytic therapy; however, it is also part of the natural evolution of cerebral infarction. The ECASS investigators divided hemorrhage into a radiologic classification, where hemorrhagic ischemia (HI) described petechial hemorrhage without mass effect, and parenchymal hematoma (PH) denoted hematoma with mass effect. Both HI and PH are further sub-classified into whether hemorrhage involves less (HI1 and PH1) or more than 30% (HI2 and PH2) of the infarcted tissue.

Multiple risk factors are known for the development of hemorrhagic transformation, including baseline stroke severity [52,53], time to reperfusion [54], thrombolytic protocol violations [39,40], rtPA treatment [38,51,52], white matter disease burden [55], aspirin [51] and heparin use [56]. Disruption of blood–brain barrier integrity is considered focal to the development of hemorrhagic transformation. A two-phase CTP acquisition allows for permeability surface area product (PS) maps to be acquired [57]. PS is used to assess the rate of contrast agent extravasation from the intravascular to the extravascular space through a disrupted blood–brain barrier [58]. Contrast agent extravasation leads to prolonged enhancement of the tissue beyond the intravascular or first phase of a CTP study; therefore, requiring a two-phase acquisition for PS determination.

Aviv et al. demonstrated a significantly higher ischemic PS region in patients with hemorrhagic transformation compared with those without [57]. A PS threshold of 0.23 ml/min/100 g enabled differentiation between those patients undergoing hemorrhagic transformation (Figure 2) and those who did not (Figure 3). No significant difference in ischemic severity measured by cerebral blood flow (CBF) was found in the two groups. Patients treated with rtPA were more likely to have hemorrhagic transformation; however, there was no significant difference in PS between the rtPA- and non-rtPA-treated patients.

- **Primary intracerebral hemorrhage**

  Intracerebral hemorrhage accounts for 10–30% of all strokes [59] with outcomes significantly worse than with ischemic stroke. Up to 50% mortality at 30 days has been documented [60], and hematoma size has been demonstrated to be one of the most important predictors of 30 day mortality [61]. Hematoma expansion is also highly predictive of neurological deterioration [62–64] and is an independent predictor of mortality and functional outcomes [65]. Clinical risk factors for hematoma expansion include hyperglycemia [64,66], hypertension [67] and anticoagulation [68–70]. The CTA spot sign has been described by several authors as a reliable marker of hematoma expansion and poor clinical outcome (Figure 4) [71–73]. This CTA spot sign is defined as one or more foci of contrast density within the hematoma — usually twice that of hematoma background — not communicating with vessels beyond the hematoma margin on CTA source images (Figure 5) [71]. However, a small number of hematomas continue to expand in the absence of a CTA spot sign. Ederies et al. demonstrated contrast accumulation, termed postcontrast leakage (PCL), within a hematoma on postcontrast CT performed after initial CTA was associated with hematoma expansion [74]. Patients with PCL and a CTA spot sign tended to have larger absolute hematoma expansion and demonstrated larger initial hematoma volumes. However, in 60% of patients demonstrating only PCL, a significant hematoma expansion was also documented. Recombinant
factor VIIIa is a treatment option for reducing hematoma expansion, and is currently under investigation within a multicenter NINDS funded study, the CTA Spot Sign for Predicting and Treating Intracerebral Hemorrhage Growth (STOP-IT) study. Recombinant factor VIIIa is associated with thrombotic risks and it is expected that the CTA spot sign may help identify patients who would benefit the most from this type of treatment.

### Advances in understanding clot burden & vascular recanalization
Recanalization is the main target of stroke treatment strategies to reduce tissue at risk and reverse neurologic deficits. Revascularization first depends on recanalization of the primary arterial occlusive lesion, but also on reperfusion of the distal vascular bed [75, 76].

The success of recanalization is dependent upon the clot composition, thrombolytic technique, clot

![Figure 2. Increased CT permeability predicts hemorrhagic transformation.](image)

(A) Noncontrast CT demonstrates a subtle loss of gray–white matter differentiation at the posterior left frontal lobe. Subtle sulcal effacement is also seen. (B) The CT perfusion cerebral blood flow map demonstrates corresponding ischemia in the left frontal lobe. (C) The permeability surface area product map shows superimposed ischemic region of interest (ROI) and contralateral mirror ROI. Permeability surface area product values in ischemic and mirrored ROIs are increased relative to contralateral. (D) The corresponding day 5 MRI gradient T2 sequence shows susceptibility in ischemic area consistent with hemorrhagic transformation.
burden and location, and collateral supply [77–81]. Larger, more proximal clot is harder to treat and leads to worse clinical outcomes compared with smaller, more distally located clot [78,81–83]. This has been demonstrated indirectly with patient's having a hyperattenuated middle cerebral artery sign, larger final infarct volumes and worse functional outcomes [80]. Larger, more proximal clot burden involving the distal internal carotid and the middle cerebral artery have been demonstrated to have even lower early recanalization rates and worse neurologic improvement rates compared with middle cerebral artery occlusion alone [84].

The concept of clot burden has been indirectly examined using the hyperattenuated arterial sign on NC-CT [78,85,86], and more directly via conventional angiography [87]. CTA provides a widely available and rapid assessment of intracranial and cervical circulation, allowing for the evaluation of the extent of clot. A grading system or clot-burden score has been developed, using a scale of 0–10 (Figure 6) [88]. A score of 10 is normal, implying clot absence. A score of 2 is subtracted for thrombus in each of the supraclinoid internal carotid arteries (ICAs), the proximal half of the MCA trunk, and the distal half of the MCA trunk. A
score of 1 is subtracted if thrombus is found in the infraclinoid ICA, proximal anterior cerebral artery (A1 segment) and for each affected proximal M2 branch (up to two branches). A score of 0 infers complete multisegment vessel occlusion.

Collateral blood supply through peripheral leptomeningeal sources is also important and has been demonstrated to correlate with smaller final infarct volumes [77,89]. Evaluation of collateral blood supply can be a challenge, often due to the small vessel size and complex routes [90]. A grading system of collateral blood flow using conventional angiography demonstrated a significant correlation between the degree of collateralization and favorable outcomes [91,92]. The presence of collateral circulation was the only radiologic predictor of favorable outcomes in one study [92]. A grading system using multidetector CTA has also been developed (Figure 7), which grades the degree of leptomeningeal collateral blood supply in the MCA territory [93]. A score of 0 infers complete absence of collateral supply in the occluded MCA territory. A score of 1 indicates collateral supply filling 0–50% of the affected territory, and a score of 2 indicates 50–100% collateral supply of the affected territory. A score of 3 indicates 100% collateral supply of the affected territory.

Increasingly, CTA is being used in the primary assessment of patients presenting with acute stroke. The goal is to gather as much information as possible, particularly pertaining to vascular anatomy and to the site and degree of vascular occlusion prior to thrombolytic therapy. The clot burden and collateral blood supply scoring systems provide additional information in the prediction of stroke outcome. The clot burden score is an independent predictor of clinical and radiologic outcomes in acute MCA territory stroke [88]. Patients with smaller clot burden are more likely to have smaller baseline infarcts, lower baseline NIHSS scores, achieve good clinical outcomes and have smaller final infarct sizes. Following intravenous rtPA therapy, patients with smaller clot-burden also demonstrate higher revascularization rates [88].

A clot burden score threshold of less than 6 has a modest sensitivity (73%) and specificity (64.6%) for predicting good clinical outcomes. These patients had higher baseline ASPECTS, smaller CBV and CBF volumes, higher collateral blood supply score and smaller final infarct size.

The collateral blood supply score, although not able to independently predict clinical outcomes, was able to predict final infarct size [88]. In the absence of adequate collateral flow, irreversible neuronal damage occurs within minutes [94]. Collateral supply helps to prevent or limit the degree of infarction until recanalization allows ischemic penumbra reperfusion [92]. It therefore follows that good collateral blood supply can predict smaller infarct volumes.

Increasingly advanced imaging techniques are being used to stratify patient risk for stroke management strategies [47,95]. Proximal clot location is increasingly felt to be an important determinant in outcome [78,96–98], with patients

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Figure 4. CT angiographic spot sign. (A) Noncontrast CT demonstrating large left frontal and basal ganglia primary intracranial hemorrhage with mild surrounding edema, and associated rightward midline shift, subfalcine herniation and intraventricular hemorrhage. (B) CT angiography (CTA) demonstrates area of contrast enhancement within the hemorrhage (arrow), consistent with the CTA spot sign. (C) CTA coronal reformat demonstrates the complexity of the CTA spot sign appearance on multiplanar visualization and the extent of contrast enhancement within the hematoma.
with larger clot burdens having larger infarction volumes and poor clinical outcomes \cite{99,100}. Multiple recanalization techniques are available, including intravenous and intra-arterial thrombolysis, mechanical thrombectomy devices, and low-frequency pulsed-waved transcranial Doppler sonography \cite{82,83,101,102}. Recanalization rates do vary depending on location and extent of thrombus. Occlusion length has been demonstrated to be an important factor in the efficacy and complication rate of mechanical thrombectomy \cite{81}. More invasive techniques offer the benefit of higher recanalization rates, however, at the expense of increased complications, such as parenchymal hemorrhage \cite{103} or vessel injury/rupture \cite{104}. Recanalization rates utilizing intravenous rtPA are only 9% for combined ICA and MCA occlusions, compared with 39% for isolated MCA occlusions \cite{84}. Patient stratification utilizing tools, such as clot burden scores, ASPECTS, NIHSS scores and CTP data, can help identify patients with a larger thrombus extent and, therefore, help select patients who may benefit from more aggressive recanalization strategies.

**Advances in imaging thresholds & predictors of tissue fate**

The term ischemic penumbra is defined as a region of hypoperfused, electrically silent and functionally impaired but viable tissue \cite{94}. This penumbra or tissue at risk of infarction has been a primary goal of neuroimaging techniques to identify. rtPA is currently the only drug approved for acute stroke treatment in North America. By clot lysis, this medication works to restore blood flow to ischemic regions, thereby potentially salvaging this at-risk tissue.

Early MRI studies identified tissue surrounding the diffusion abnormality as the ischemic penumbra using diffusion–perfusion imaging. Diffusion restriction was considered irreversibly infarcted tissue, and the remaining perfusion abnormality the ischemic penumbra \cite{105}.

![Figure 5. CTA spot sign mimic.](image-url) 

**Figure 5. CTA spot sign mimic.** (A) Noncontrast CT demonstrating right insular and putamen primary intracranial hemorrhage with associated mass effect. (B) CT angiography shows focus of enhancement along medial border of hematoma suspicious for a CTA spot sign. (C) CT angiography oblique coronal reformat shows focus of enhancement continuous with a lenticulostriate vessel. Appearances are consistent with a CTA spot sign mimic.
This diffusion–perfusion model, however, is likely to be too simplistic. Firstly, the perfusion abnormality often overestimates final infarct volume [106], thereby overestimating the tissue at risk. Secondly, the diffusion abnormality is not necessarily irreversibly infarcted tissue, with some studies demonstrating reversibility with early revascularization [107,108]. Using these concepts, Kidwell et al. developed a modified model of the ischemic penumbra in which the penumbra includes the diffusion–perfusion mismatch region (minus the region of benign oligemia) as well as a portion of the initial diffusion abnormality itself [109].

Despite advances in MRI imaging techniques, CT remains the most widely available and used imaging modality in acute stroke. CTP data utilizing CBF and CBV maps have also been demonstrated to be able to identify the ischemic penumbra [29,30,110]. A CBF threshold of 25 ml/min/100 g has been correlated with tissue progressing to infarction in the absence of recanalization [111,112]. CBV values tend to remain constant or even slightly increase in the ischemic penumbra and fall in areas of infarction. Utilizing CBF and CBV thresholds in isolation to identify the ischemic penumbra have not been highly accurate, prompting the use of logistic regression and multivariate analysis to identify ways of increasing the sensitivity and specificity of penumbra identification. One such method identified an interaction between CBF and CBV that provided maximum separation between penumbra and infarcted tissue in gray matter. Any combination of CBF and CBV values above the derived threshold of 31.3 were classified as penumbra, and below this value as infarction. The model demonstrated a sensitivity, specificity and overall accuracy of 97.0, 97.2 and 97.1%, respectively, for infarct detection [112]. The model focuses on the CBF and CBV alterations to characterize the ischemic penumbra, and the matched decrease in both parameters in areas of infarction [110,113]. Given that infarct CBF values are slightly lower, and CBV values much lower in infarcted than penumbral tissue, the product of these two values maximizes the separation between these two entities.

Perfusion and diffusion thresholds for infarction are likely to be different between gray and white matter [114–118]. A CBF threshold of 14 ml/min/100 g was shown to correlate well with final white matter infarct volume in the absence of recanalization [116,118,119]. The same model described for identifying gray matter penumbra has also been applied to white matter. Using logistic regression analysis, the threshold of 8.14 was identified for determining infarction from ischemic penumbra in white matter with a sensitivity, specificity and overall accuracy of 95, 94 and 95%, respectively (Figure 8) [118]. The same authors determined thresholds using CBV and CBF values in isolation. A CBV threshold of 0.82 ml/100 g resulted in a sensitivity and specificity for final infarct of 76 and 88%, respectively; however, there was significant overlap between the penumbra and final infarct regions. Using a CBF threshold resulted in slightly higher sensitivity and specificity of

![Collateral score](image-url)

**Figure 7. Collateral score.** (A) CS = 0, infers complete absence of collateral supply in the occluded middle cerebral artery territory. (B) CS = 1, indicates collateral supply filling 0–50% of the affected territory. (C) CS = 2, indicates 50–100% collateral supply of the affected territory. (D) CS = 3 indicates 100% collateral supply of the affected territory. CS: Collateral score.
81 and 91%, respectively; however, significant overlap between the penumbra and final infarct regions was still observed.

An observed increased CBV in the ischemic penumbra can be explained by direct cerebral autoregulatory responses to maintain CBF by dilating precapillary vessels in response to the decreased perfusion pressure [120]. However, reduced CBV in infarcted tissue is not completely understood [22,29,110,113]. A possible explanation for a matched decrease in CBF and CBV involves failure of autoregulation in response to severe hypoperfusion [120]. Metabolic mechanisms, such as neuronal death resulting in significantly elevated extracellular potassium concentrations and vasoconstriction, have also been proposed [121].

**Conclusion**

There have been many advances in the imaging of acute stroke in recent years. The identification of stroke on NC-CT has improved by identifying

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**Figure 8. Prediction of tissue fate from baseline perfusion imaging.** (A) Noncontrast CT obtained 5–7 days following stroke showing a final infarct outlined in yellow. This is superimposed on (C & D). (B) Shows an average-weighted image used to create a white matter mask with a Hounsfield unit threshold. (C) White matter is classified according to cerebral blood flow (cerebral blood flow of 0–14 ml/min/100 g is shown in dark blue; cerebral blood flow of 14–100 ml/min/100 g is shown in light blue). Penumbra is identified as ischemic white matter tissue that did not show infarction of the 5–7 day noncontrast CT (black outline in (C & D) and is superimposed on the cerebral blood flow image (D)).
EIS and systematically assessing for stroke by using ASPECTS. Sensitivity and specificity have further improved by using CTA-SI and CTP data to identify the presence of infarction.

In the unselected patient, thrombolytic therapy with rtPA improves clinical outcomes up to 4.5 h following symptom onset. It remains to be determined whether a selected patient with an identifiable ischemic penumbra may benefit beyond this treatment time window.

Hemorrhagic conversion risk can be predicted by assessing the blood–brain barrier using a two-phase CTP acquisition and acquiring PS data. In cases of primary intracerebral hemorrhage, hematoma expansion can be predicted by using the CTA spot sign and PCL. Assessing the extent of clot burden and degree of collateral blood supply not only aids in the prediction of clinical outcomes, but helps select patients who may benefit from more aggressive thrombolytic therapies, such as intra-arterial rtPA or mechanical thrombectomy. Cerebral blood flow thresholds for both gray and white matter that can predict the final volume of infarction in the absence of recanalization have been identified. Using the interactions between CBF and CBV data allow accurate determinations of the ischemic penumbra and salvageable brain tissue if recanalization occurs. Acute stroke imaging assessment now offers a wealth of information to the clinician by identifying the presence and extent of infarction, predicting hemorrhagic transformation and hematoma expansion, selecting patients for more aggressive thrombolytic therapy and identifying the presence of ischemic penumbra, ultimately, predicting clinical outcomes. This information may help promote a shift from treating the unselected stroke patient to individualizing stroke therapy and selecting patients who may benefit from aggressive thrombolysis beyond the current treatment time window.

**Future perspective**
Acute stroke imaging will continue to evolve in the coming years. This will include a more widespread use and implementation of the advanced imaging techniques described. A standard NC-CT will no longer be acceptable as an acute stroke workup. With the extensive information that comes from the use of CTA-SI and CTP, the detection and evaluation of the extent of infarction will be much more accurate. Using PS maps more routinely will allow the prediction of hemorrhagic conversion, thus allowing risk stratification prior to thrombolytic treatment.
Physiological imaging using CBF and CBV thresholds will allow an accurate assessment of the ischemic penumbra regardless of the time from symptom onset. Future work will no doubt study thrombolytic therapy in patients who demonstrate a persistent penumbra beyond the 4.5 h treatment time window. These selected patients will hopefully benefit from thrombolysis well beyond the current time constraints, thus opening thrombolytic therapy to a much larger patient population.
Additional thrombolytic agents will also likely be approved for clinical use. More fibrin specific agents, such as desmoteplase, may show clinical benefit specifically in the extended treatment time window.

**Executive summary**

**Advances in the prediction of stroke**
- Infarct detection is improved with the use of Alberta Stroke Program Early Computed Tomography Score (ASPECTS) and identifying early ischemic signs on noncontrast CT. Sensitivity and specificity of stroke detection and extent determination are significantly improved by using CT angiography source images and CT perfusion.
- The treatment time window for recombinant tissue plasminogen activator thrombolysis is now 4.5 h from time of symptom onset in the unselected patient.
- Hemorrhagic conversion of infarct can be predicted by using permeability surface area product maps.
- Primary intracerebral hemorrhage hematoma expansion can be predicted by the presence of the CT angiography spot sign and postcontrast leakage.
- The clot burden score and collateral supply score can predict clinical outcome and final infarct size, respectively, and both may help select patients for more aggressive thrombolytic techniques.
- A threshold using an interaction between cerebral blood flow and cerebral blood volume values can identify the ischemic penumbra.

**Future perspective**
- Future stroke treatment will likely be more individualized with a more personalized risk stratification. Physiological imaging of the ischemic penumbra may help identify selected patients who would benefit from thrombolysis beyond 4.5 h.
Extending the treatment time window will also allow more routine intra-arterial treatment options for acute stroke. The use of current and new thrombolytic agents and continued evolution of mechanical thrombectomy devices will surely be seen.

Acute stroke imaging and treatment will continue to grow and evolve; however, the effective implementation and management of this information will likely be an ongoing challenge for most institutions. Acute stroke teams not only require easy access to advanced stroke imaging and stroke neurology care, but also the continued support from emergency department personnel and medical transport personnel, not to mention anesthesia and angiography support. The effectiveness of an acute stroke team will be dependent upon its weakest point and will serve as an ongoing focus of improvement for successful stroke treatment.

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Using CT perfusion data improves the sensitivity and specificity of both stroke detection and extent of infarction and is predictive of good clinical outcome using an Alberta Stroke Program Early CT Score threshold of 8.

Hemorrhagic conversion risk can be predicted using a two-phase CT perfusion study to assess blood–brain barrier integrity using permeability surface area product maps.


* The CT angiography spot sign can predict hematoma expansion in primary intracerebral hemorrhage.


* Clot burden score and collateral blood supply score can predict clinical outcomes and final infarct size, respectively, and may help select patients for more aggressive thrombolysis.


Ischemic penumbra can be identified using CT perfusion data and using a threshold derived from the interaction between cerebral blood flow and cerebral blood volume values.

