



THE ROLE OF CT IMAGING TECHNIQUES IN THE ACUTE STROKE PATHWAY



Time is of the essence in the diagnosis and management of acute ischemic stroke

Acute stroke is a neurovascular emergency that requires rapid diagnosis and treatment.¹ Left untreated, patients could die or suffer devastating neurologic disabilities.¹

Because all patients require imaging to establish the stroke type diagnosis (ischemic vs. hemorrhagic) prior to treatment, any delays in thrombolytic or endovascular therapies are associated with unfavorable clinical outcomes.² Every minute in which a large vessel ischemic stroke is untreated, the average patient loses 1.9 million neurons, corresponding to an accelerated aging of more than 3 weeks.³

Neuroimaging plays a vital role in the workup of acute stroke

Among neuroimaging modalities, computed tomography (CT) provides essential information to accurately triage patient and guide treatment decision-making that can improve outcomes in patients presenting with acute stroke.⁴

Multiple techniques of CT imaging can now be acquired easily, quickly and around the clock. But the integration of information from CT imaging and clinical features of acute stroke, to guide the correct triage and/or treatment decision, requires specialized expertise. Large disparities in the availability of such specialized expertise exist across health systems, resulting in significant inefficiencies in the delivery of acute stroke care.

During the last two decades, with the improved understanding of stroke imaging and therapeutics, stroke pathways have significantly progressed. With clinical trial

data demonstrating that treatment is not only possible, but also successful in a wide range of stroke patients, practice is now changing.¹

In 1995, intravenous thrombolysis was shown to be effective for acute ischemic stroke (AIS) management within 3h of symptom onset.⁵ Subsequent studies, using next generation CT with simple non-contrast CT-based patient selection, extended the time window to 4.5h.⁵ Recent work using either multimodal CT or multimodal magnetic resonance imaging (MRI) has demonstrated the efficacy of intravenous thrombolysis for patients with stroke-on-awakening or unwitnessed stroke and stroke within 9 hours of symptom onset.^{6,7}

Since 2015, endovascular thrombectomy is increasingly used for the management of acute ischemic stroke due to proximal large vessel occlusion. Advanced imaging techniques have enabled the selection of patients suitable for treatment in a window up to 24 hours from last known well (including unwitnessed stroke/stroke-on-awakening).¹

In parallel with clinical evidence advances, guidelines for stroke management (NICE, Canadian Best Practice Recommendations for Stroke Care, ESO guidelines, AHA Stroke guidelines)⁸⁻¹¹ are progressively evolving.

Thanks to a better understanding of CT imaging, stroke management has improved and patients selected with CT imaging can now be promptly and successfully treated.¹



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ADVANCES IN CT IMAGING AT THE ROOT OF THE EVOLUTION OF STROKE MANAGEMENT

Brain tissue ischemia is a dynamic process that is tolerated differently by each patient.¹² Cerebral reserve, collateral circulation, tissue propensity to ischemia, ischemia duration and vessel occlusion status all play a part in tissue fate.

New contrast CT and MRI technologies are now capable of accurately assessing this dynamic process.¹² CT-based imaging can now estimate:

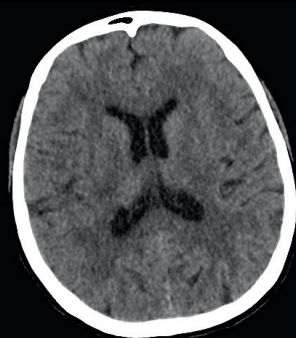
- Brain tissue that is already infarcted
- Brain tissue that is highly likely to infarct even with ultra-early reperfusion (predicted ischemic core)
- Brain tissue that is likely to infarct in the time it takes to achieve reperfusion (predicted core growth over time)
- Penumbra (tissue predicted to progress to infarction if adequate blood flow is not restored within a given time).

» Non-Contrast CT (NCCT)

NCCT is widely available and very sensitive in detecting hemorrhage.⁵ It is recommended as first-line for some time in all patients with suspected acute stroke to identify the presence of stroke and the type of stroke (ischemic or hemorrhagic origins).^{8,9,11} In addition, NCCT, especially thin slice CT, can detect large vessel occlusions with high sensitivity and specificity. NCCT can also be used to detect sub-acute looking ischemic stroke, a marker of hemorrhage risk with thrombolysis. NCCT also allows to detect and quantify the early ischemic changes thanks to the ASPECT score (**A**lberta **S**troke **P**rogram **E**arly **C**T).⁵ The ASPECTS is a scoring system dividing the MCA territory into 10 zones, one point is subtracted for early ischemic change in each zone.¹³ A score of 10 indicates a normal CT scan without any sign of ischemic change, but a score of 0 indicates diffuse ischemic changes in the entire MCA territory.¹³

NCCT head of patient with acute ischemic stroke

IMAGES COURTESY OF DR. NIEBOER FROM UZ BRUSSELS, BELGIUM



» CT angiography (CTA)

Head and neck CTA is a contrast-enhanced imaging technique. It is quick to perform and has a high sensitivity and specificity for the detection of intracranial artery occlusion.^{1,5} CTA can demonstrate the location of the large vascular occlusion (LVO), defining the need for acute revascularization using endovascular thrombectomy.⁴ CTA has revolutionized stroke practice.¹⁴

In the acute stroke pathway, CTA follows NCCT and is recommended to detect or confirm vessel thrombosis in all stroke syndrome presentations.^{8,9,11} The demonstration of an intracranial occlusion is a precursor to endovascular thrombectomy in all time windows from stroke onset.

Thrombus characterization is predictive of treatment success for patients with acute ischemic stroke.^{11,15,16} CTA helps identify location and size of thrombus. Large thrombus in proximal locations, such as in the internal carotid artery, are less likely to recanalize using intravenous alteplase. CTA also helps estimate thrombus permeability and identifies non-occlusive thrombus; permeable thrombus is more likely to recanalize early with intravenous thrombolytics like alteplase.¹⁵

“ In the acute stroke pathway, CTA is recommended to detect or confirm vessel thrombosis in all stroke syndrome presentations. ”

CTA also provides important information on pial collateral circulation. Patients with good collaterals are likely to benefit from thrombolysis/thrombectomy vs. patients with poor collaterals. The ESCAPE* and ESCAPE NA1 trials have used collateral imaging techniques for patient selection.^{17,18} Current guidelines recommend considering the assessment of the collateral flow status to determine eligibility for mechanical thrombectomy.^{5,9,11}

Single phase CTA

Single phase CTA is used to identify the presence of large vessel occlusions, the target for endovascular treatment, with a high sensitivity and specificity.¹ It provides high-resolution images.¹⁹

Single phase CTA is a rapid, easily available imaging tool, but it does not have temporal resolution and may lead to the risk of mislabeling pial arterial filling.^{2,4,19}

A potential pitfall of single-phase CTA is the risk of suboptimal opacification of the smaller distal collateral vessels.²⁰

In addition, slow flow within the proximal large arteries, due to a high-grade proximal stenosis for example, may falsely give the impression of an occlusion.

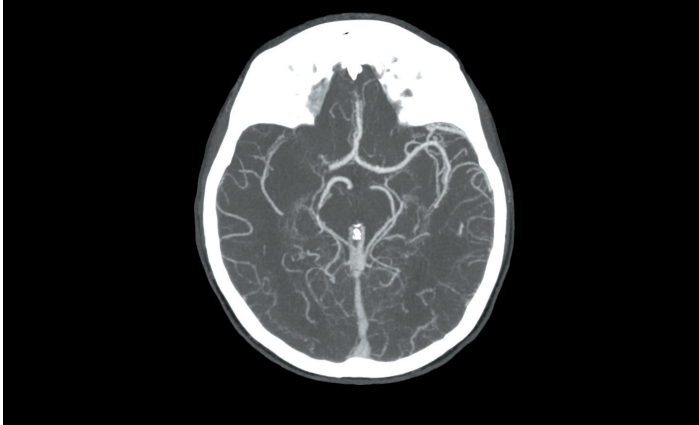
* ESCAPE: Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke.



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CTA demonstrating an occlusion of the right middle cerebral artery

IMAGES COURTESY OF DR. NIEBOER FROM UZ BRUSSELS, BELGIUM



Multiphase CTA

The aim of multiphase CTA (mCTA) is to quickly and reliably identify brain potentially salvageable with intervention. It provides an assessment of the occlusion location and the degree and extent of pial arterial filling in the whole-brain in a time-resolved manner; pial collateral status on mCTA being an independent predictor for clinical outcome after acute ischemic stroke.^{1,2, 16,21}

Multiphase CTA can also be used to estimate ischemic core, its growth over time and penumbra.²² In addition, mCTA provides better estimates of thrombus extent and permeability than single phase CTA.^{23,24}

This technique is quick to perform and provides three time-resolved images of pial arterial filling in the whole brain, unlike conventional single-phase CTA.² Acquisition of four time-resolved images can be used for patients with predicted poor cardiac output or to acquire mid- to late venous phase images for the uncommon suspected venous occlusion stroke syndromes.

“ Multiphase CTA provides an assessment of the occlusion location and the degree and extent of pial arterial filling in the whole-brain in a time-resolved manner; pial collateral status on mCTA being an independent predictor for clinical outcome after acute ischemic stroke. It can also be used to estimate ischemic core, its growth over time and penumbra, and provides better estimates of thrombus extent and permeability than single CTA. ”

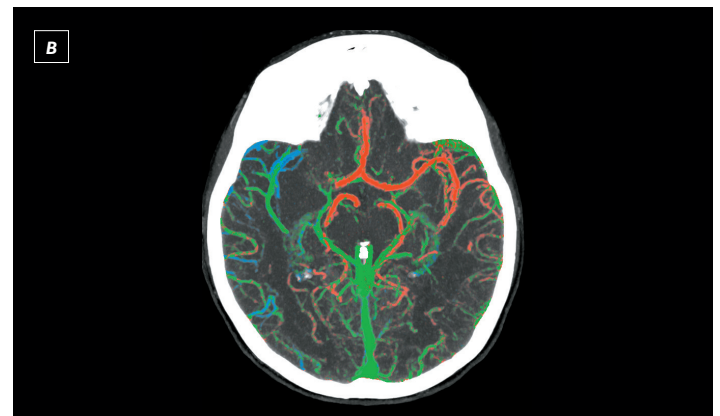
mCTA is less vulnerable to patient motion than CT perfusion. It requires lower radiation dose, no additional administration of contrast agent and yields images that are easy to acquire and interpret.^{1,2,16}

Furthermore, mCTA has been shown to be reliable and have higher inter-rater agreement than single phase CTA for grading collateral status.^{2,16}

A: Multiphase CTA images in a patient with a proximal right middle cerebral artery occlusion and good collaterals;

B: ColorViz results from the fusion of all CT phases. Vessels are colored depending on the distribution of contrast enhancement (Red: Pre-venous phase; Green: Venous phase; Blue: Post-phase).

IMAGES COURTESY OF DR. NIEBOER FROM UZ BRUSSELS, BELGIUM Using FastStroke (GE Healthcare, Milwaukee, Wisconsin)



» CT perfusion (CTP)

CTP has been developed to estimate the predicted physiology of ischemia mimicking PET imaging for the analysis of the infarct core and ischemic penumbra.⁵ CTP is currently recommended to select patients with AIS, within 6 to 24 hours of the last known well time, who have large vessel occlusion in the anterior circulation for mechanical thrombectomy.^{9,10,11}

CT perfusion is a dynamic contrast-enhanced imaging technique, from which various parameters that represent the current perfusion status of the brain tissue can be calculated.¹ It provides information about blood flow in brain tissue.

CT perfusion is used to predict ischemic core, its growth over time and penumbra.¹

CTP can be performed rapidly²⁰ and perfusion maps are generated by post-processing softwares.² CTP can also be used to estimate the risk of hemorrhage with thrombolysis or thrombectomy and to measure thrombus permeability.²⁹



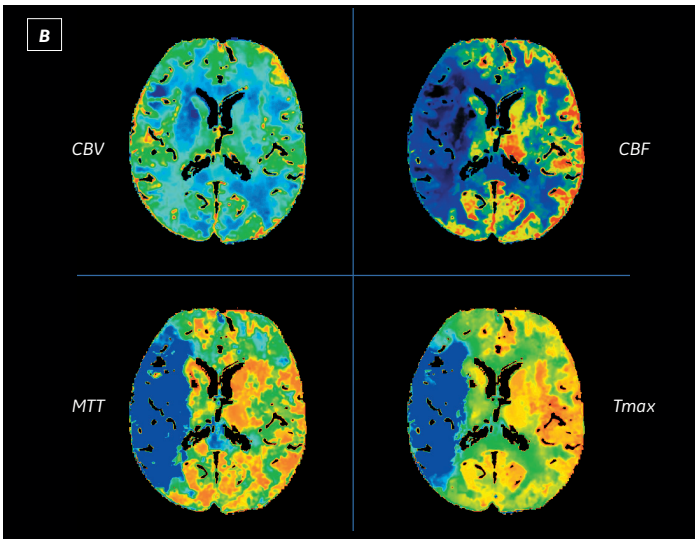
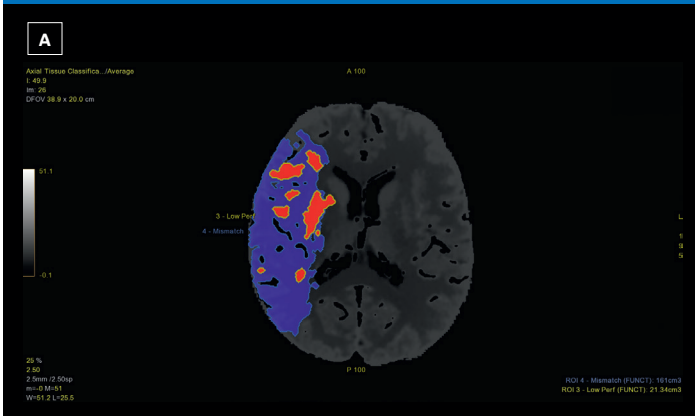
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“ CTP is used to predict ischemic core, its growth over time and penumbra, and can also be used to estimate the risk of hemorrhage with thrombolysis or thrombectomy. ”

A: Based on CT Perfusion, tissue classification map displays in red the Low Perfusion region (predicted infarct core) and the Mismatch region (predicted penumbra) in blue.

B: Functional maps assess perfusion parameters: cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and Tmax.

IMAGES COURTESY OF DR. NIEBOER FROM UZ BRUSSELS, BELGIUM
Using FastStroke (GE Healthcare, Milwaukee, Wisconsin)



All CT techniques, from single- or multiphase CTA to CT perfusion, have demonstrated their value as they have been included in key clinical studies to select patients for acute stroke therapy.

KEY CLINICAL STUDIES DRIVING THE EVOLUTION OF STROKE CARE

» Evolution of imaging techniques supporting the treatment window extension

The results of key clinical trials, published since 2014, have established endovascular treatment as the new standard of care for acute ischemic stroke due to large vessel occlusion (LVO).^{1,17,25-28}

All of these trials used CT imaging for patient selection, up to 8h to 12h from the last known well time (see table). NCCT and CTA were used to select patients with severe deficit and low infarct volume from LVO in most of the clinical trials.⁵ CTP was used for patient selection to assess infarct core or ischemic penumbra in two of the trials.

The **MR CLEAN*** trial showed that, in patients with acute ischemic stroke due to a proximal intracranial occlusion of the anterior circulation, intra-arterial treatment administered within 6 hours after stroke onset was effective and safe.²⁵ In this trial, **patients were selected using NCCT plus either single phase CTA, magnetic resonance angiography (MRA), or digital-subtraction angiography.**²⁵

The **ESCAPE**** trial used NCCT and CTA as radiographic markers to enroll patients up to 12 hours from symptom onset (defined as the last known well time).¹⁷ NCCT and CTA (multiphase in a majority of patients) were performed to identify participants with a small infarct core, an occluded proximal artery in the anterior circulation, and moderate-to-good collateral circulation.³⁰ The results showed that a rapid endovascular treatment improved clinical outcomes and reduced mortality, so much so that the trial was stopped early.¹⁷

This imaging approach in which collateral vessel imaging with mCTA was used to improve the assessment accuracy of early ischemic changes seen on unenhanced CT images, resulted in a low number of imaging protocol violations and enabled the meeting of workflow time targets.¹⁷ In addition, the ESCAPE trial enrolled patients in the 6-12 hours from stroke onset. Although, only 49 patients were enrolled in this time window with the NCCT and mCTA paradigm, the treatment effect size was similar to patients enrolled in the 0-6 hour time window. **Thus, the ESCAPE trial imaging protocol provided a unique perspective on patients presenting to medical attention relatively late.**³⁰

* MR CLEAN: Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands

** ESCAPE: Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke



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In parallel, the EXTEND-IA and SWIFT-PRIME trials used CT perfusion imaging based selection algorithms and showed higher rates of good functional outcomes compared to trials that used other strategies to select patients.³¹

The **EXTEND-IA***** trial was a smaller phase 2 study with a primary reperfusion outcome at 24 hours. It involved patients with anterior circulation ischemic stroke and a large artery occlusion (internal carotid artery or the first or second segment of the middle cerebral artery), **as seen on CTA.²⁶ CT perfusion imaging was also used before randomization to identify potentially salvageable brain tissue.** The results showed that early thrombectomy combined with intravenous thrombolysis, provided higher reperfusion, early neurologic recovery, and better functional outcomes compared to thrombolysis alone.²⁶

The **SWIFT-PRIME°** trial included patients who had acute ischemic stroke with moderate-to-severe neurologic deficits and an imaging-confirmed occlusion in the proximal anterior intracranial circulation (CTA or MRA).²⁷ Principally, **perfusion imaging and in some cases mCTA were used to identify patients with salvageable tissue.** The results showed that intravenous thrombolysis combined with a thrombectomy with a stent retriever within 6 hours of stroke onset improved functional outcomes at 90 days.²⁷ These results provided evidence that **CTP imaging used to estimate the volume of irreversibly injured ischemic tissue and the volume of brain tissue that is ischemic but not yet infarcted, selects patients with a high probability of benefit from fast endovascular treatment.**³¹

The **REVASCAT°°** trial aimed to assess the safety and efficacy of thrombectomy in **patients with acute stroke caused by a proximal LVO and an absence of a large infarct on baseline CT and CTA imaging.**²⁸ The trial required the use of CTP in the subset of patients enrolled in the 6-8 hour time window. Overall, the results showed that a mechanical thrombectomy with the solitaire stent retriever was safe and led to improved clinical outcomes, as compared with medical therapy alone and could be placed up to 8 hours after symptoms onset.

The **THRACE°°°** trial enrolled patients with moderate-to-severe stroke due to an occlusion of a proximal cerebral artery, within 4h of symptom onset, confirmed by CTA or MRA.³² **A large majority of patients were enrolled on**

the basis of MR imaging. In these patients, mechanical thrombectomy combined with standard intravenous thrombolysis provided a significantly higher rate of functional independence at 3 months, with no evidence of increased mortality, compared to intravenous thrombolysis alone. These results suggest that **multimodal MR imaging could also be used to select patients for endovascular treatment in the anterior circulation.**³²

In the **PISTE#** trial, **CTA or MRA were used to show an occlusion of a large anterior circulation artery.**³³ This trial was conducted in the UK and halted prematurely in the light of positive MR CLEAN results. It demonstrated that proceeding as fast as possible to thrombectomy after CTA confirmation of a large artery occlusion on a background of intravenous thrombolysis is safe, improves clinical outcomes and, in the per-protocol population, improves disability-free survival.³³

“ Clinical trials published between 2015 and 2016, have allowed to safely extend the treatment window for patients with acute ischemic stroke. ”

» The late window trials

In 2018, results of the DAWN and DEFUSE 3 studies provided evidence that imaging signature, rather than time from stroke onset (or last known well time) could be used to expand treatment eligibility.⁶ These 2 major trials assessed the benefit of endovascular treatment in image-selected patients presenting in late time windows: 6–24 hours in DAWN and 6–16 hours in DEFUSE 3.^{31,34}

The **DAWN##** trial included patients at a median of 12.5h from last-known-well (88% of patients had unwitnessed stroke or stroke-on-awakening). It showed that, among patients with stroke due to occlusion of a large artery who had last been known to be well 6 to 24 hours earlier, and who had a mismatch between the severity of the clinical deficit and the infarct volume assessed by diffusion-weighted MRI or perfusion CT, outcomes for disability and functional independence at 90 days were better with thrombectomy plus standard medical care than with standard medical care alone.³⁴

*** 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 for Acute Ischemic Stroke

°° REVASCAT: Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset

°°° THRACE: THROmbectomie des Artères CErebrales

PISTE: Pragmatic Ischaemic Thrombectomy Evaluation

DAWN: DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo



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Therefore, the time from stroke onset can be replaced by careful imaging-based patient selection on the basis of a disproportionately severe clinical deficit in comparison with the size of stroke on imaging.³¹ Time becomes simply another variable to consider rather than a hard threshold that determines treatment eligibility.

The **DEFUSE 3^{###}** trial was designed to test the hypothesis that patients who were likely to have salvageable ischemic brain tissue would have better functional outcomes if they underwent endovascular therapy 6 to 16 hours after they were last known to have been well (50% of patients had stroke-on-awakening) versus patients treated with standard medical therapy.³¹ **The salvageable ischemic brain tissue was identified by perfusion imaging.** This trial only included patients who had findings on perfusion imaging of a penumbral tissue. The results were concordant with the DAWN trial demonstrating less disability and higher rates of functional independence at 3 months compared to standard medical therapy alone.

“ Another breakthrough came in 2018 with the late window trials demonstrating the possibility to expand treatment eligibility based on imaging signature, in particular a good collateral status. ”

» Latest developments in stroke care

In 2019, the WAKE-UP and EXTEND trials showed that thrombolysis guided by imaging (MRI and CTP respectively) is safe and effective for up to 9 hours from stroke onset/last known well time.

The **WAKE-UP⁵** trial aimed to determine whether patients with stroke with an unknown time of onset and features suggesting recent cerebral infarction on MRI would benefit from thrombolysis with the use of intravenous thrombolysis.⁶ **Patients had to have MRI findings of an ischemic lesion on diffusion-weighted imaging but no parenchymal hyperintensity in the corresponding region on FLAIR (fluid attenuated inversion recovery).** The median interval between last time the patient was known to be well and symptom recognition was 7h. The findings demonstrated the benefits of the treatment with a significantly better functional outcome compared to placebo at 90 days.

The **EXTEND⁵⁵** trial was conducted in patients who had ischemic brain tissue on imaging. The results, showed that

in these **patients who have salvageable brain tissue, defined by CT perfusion imaging**, an intravenous thrombolysis between 4.5h and 9h resulted in a higher percentage of patients with minor or no neurologic deficits compared with placebo.⁷ The trial was terminated early because of a loss of equipoise after the publication of positive results from the WAKE-UP trial.

“ The most recent trials have shown the benefit of stroke thrombolysis in a late treatment window (>4.5 h from stroke onset) with appropriate patient selection using imaging. ”

» CONCLUSION

Benefiting from the technological advances in imaging modalities, several clinical trials have transformed the management of acute ischemic stroke. These trials have demonstrated that endovascular intervention with mechanical thrombectomy improve functional outcomes in select patients with severe stroke and large artery occlusion. Each trial has included at least one imaging screening test, NCCT and CTA in most cases. Some studies included CTP to define infarct core and ischemic penumbra.⁵

The future of stroke imaging

Further technological research is needed to evaluate whether ischemic stroke patient sub-types benefit from therapy. The technology is now available to subselect ischemic stroke subtypes by vessel occluded, brain region, predicted stroke mechanism or other imaging classification in order to identify new treatments or further refine current treatments. Imaging processing, especially with the use of machine or deep learning algorithms, will aid in fast and reliable interpretation of stroke imaging. This has the potential to allow frontline physicians with limited expertise in image interpretation to make the best treatment decision for individual stroke patients. Further advances in neuro vascular imaging will lead to a real-world example of imaging based precision medicine for the acute stroke patient.

^{##} DAWN: DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo

^{###} DEFUSE 3: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke

⁵ WAKE-UP: Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke

⁵⁵ EXTEND: Extending the Time for Thrombolysis in Emergency Neurological Deficits



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Main characteristics of key clinical trials driving the evolution of stroke care.

Year of completion	Name	Patients enrolled	Design	Technology used for patient selection	Arms
2015	MR CLEAN ²⁵	500 patients with acute ischemic stroke caused by an intracranial occlusion in the anterior circulation artery	Randomized clinical trial	NCCT, CT, CTA, MRA, DSA	<ul style="list-style-type: none"> Intraarterial treatment + usual care Usual care alone
	ESCAPE ¹⁷	316 patients with a proximal intracranial occlusion in the anterior circulation	Randomized, open-label, controlled, blinded endpoint trial	NCCT, CTA (preferably multiphase), MRA in 1 patient	<ul style="list-style-type: none"> Endovascular treatment with the use of available thrombectomy devices + standard care Standard care alone
	EXTEND-IA ²⁶	70 patients with ischemic stroke who were receiving intravenous thrombolytic agent	Randomized open-label, blinded endpoint trial	CTA, as well as CT perfusion imaging processed with fully automated software	<ul style="list-style-type: none"> Endovascular thrombectomy with the Solitaire FR stent retriever + IV thrombolysis (IVT) IVT
	REVASCAT ²⁸	206 patients with acute stroke caused by a proximal large vessel occlusion and absence of a large infarct	Randomized, sequential, open-label, blinded endpoint trial	NCCT, CT, CTA, MRI, MRA, CTP in some patients 6-8h from onset	<ul style="list-style-type: none"> Endovascular treatment with the Solitaire stent retriever + medical therapy Medical therapy alone
2016	SWIFT-PRIME ²⁷	196 patients with disabling acute ischemic stroke who were receiving or had received intravenous t-PA	Randomized open-label clinical trial	NCCT, CTA, MRA, CTP or mCTA	<ul style="list-style-type: none"> Endovascular thrombectomy with the use of a stent retriever + thrombolysis Thrombolysis alone
	THRACE ³²	414 patients with acute ischemic stroke and proximal cerebral artery occlusion	Randomized controlled trial	NCCT, CT, MRA, mostly MR and MRA imaging	<ul style="list-style-type: none"> Mechanical thrombectomy + IVT IVT alone
	PISTE ³³	65 patients with acute ischaemic stroke with large artery occlusive anterior circulation	Randomized controlled trial	NCCT, CT, MRA	<ul style="list-style-type: none"> Additional (adjunctive) medical therapy with any operator-selected CE-marked device approved for intracranial clot removal Best medical therapy with IVT alone
2018	DAWN ³⁴	206 patients with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery who had last been known to be well 6 to 24 hours earlier and who had a mismatch between the severity of the clinical deficit and the infarct volume	Randomized, open-label, blinded endpoint trial with a Bayesian adaptive-enrichment design	CT, CTA and CTP imaging, MRA, MRI	<ul style="list-style-type: none"> Thrombectomy + standard care Standard care alone
	DEFUSE 3 ³¹	182 patients with proximal middle-cerebral-artery or internal-carotid-artery occlusion, an initial infarct size of less than 70 ml, and a ratio of the volume of ischemic tissue on perfusion imaging to infarct volume of 1.8 or more	Randomized, open-label trial, with blinded endpoint assessment	CT perfusion or MRI diffusion and perfusion scans were calculated with the use of an automated image postprocessing system	<ul style="list-style-type: none"> Endovascular therapy + standard medical therapy Standard medical therapy alone
	WAKE-UP ⁶	503 patients who had a stroke at an unknown time of onset: an ischemic lesion that was visible on MRI diffusion-weighted imaging but no parenchymal hyperintensity on FLAIR	Randomized, double blind, placebo-controlled trial	MRI examination that included diffusion-weighted imaging, FLAIR, a sequence sensitive to hemorrhage and time-of-flight MRA of the circle of Willis	<ul style="list-style-type: none"> IV thrombolysis matching placebo
2019	EXTEND ^{*7}	225 patients with ischemic stroke who had hypoperfused but salvageable regions of brain	Randomized, placebo-controlled	CTP imaging	<ul style="list-style-type: none"> Between 4.5 and 9.0 hours after the onset of stroke or on awakening with stroke: IV thrombolysis Placebo

*Trial terminated due to loss of equipoise following publication of positive results from a previous trial.

CE: Conformité Européenne (European Conformity); CT: Computed tomography; CTA: Computed tomographic angiography; DSA: Digital-subtraction angiography; FLAIR: Fluid-attenuated inversion recovery; FR: Flow restoration; IV: Intravenous; IVT: Intravenous thrombolysis; MRA: Magnetic resonance angiography; MRI: Magnetic resonance imaging; T-PA: tissue plasminogen activator.

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