Stroke 1

Current practice and future directions in the diagnosis and acute treatment of ischaemic stroke

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Even though stroke presents as a variety of clinical syndromes, neuroimaging is the most important biomarker to help differentiate between stroke subtypes and assess treatment eligibility. Therapeutic advances have led to intravenous thrombolysis with tissue-type plasminogen activator and endovascular treatment for proximal vessel occlusion in the anterior cerebral circulation being standard care for acute ischaemic stroke. Providing access to this care has implications for existing systems of care for stroke and their organisation and has reintroduced the possibility of adjuvant and neuroprotective treatment strategies in acute ischaemic stroke. The use of neuroimaging for patient selection and speed of diagnosis and delivery of treatment are the dominant themes of modern ischaemic stroke care.

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This is the first in a **Series** of three papers about stroke

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Introduction

Arterial stroke syndromes are characterised by a sudden loss of neurological function due to brain or retinal ischaemia (around 85%) or intracerebral haemorrhage (around 15%) (figures 1, 2). Venous stroke syndromes are much less common than arterial strokes (<1% of all strokes), present subacutely and are caused by cerebral venous sinus or cortical vein thrombosis. Stroke syndrome presentations can be transient or permanent and range from mild to fatal. The historical epidemiological definition differentiating transient ischaemic attacks and ischaemic stroke on the basis of the duration of their symptoms (less or more than 24 hours) is now outdated because duration does not accurately predict the pathology. MRI studies have shown that symptom duration greater than 1 h is strongly associated with irreversible ischaemia on diffusion-weighted MRI (DWI) and thus clinically defined transient ischaemic attacks might not be transient on a tissue level.[1] A transient ischaemic attack is not a pathological entity itself but rather the mildest form on the spectrum of ischaemic stroke syndrome presentations. Whereas intracerebral haemorrhage does not have a well proven acute treatment, ischaemic stroke is immediately treatable with reperfusion therapy and this Series paper will focus on the management of acute ischaemic stroke syndromes.

Ischaemic stroke is caused by a focal occlusion or stenosis of an artery or multiple arteries in the brain (intracranial occlusion) or leading to the brain (extracranial cervical artery occlusion). These focal occlusions occur because of a variety of mechanisms, including cardioembolism, artery-to-artery thromboembolism, occlusive arterial disease, and small vessel disease, whose differentiation is important for tailored secondary stroke prevention. However, detailed mechanistic information is most often neither readily available in the acute setting, nor necessarily relevant to the choice of acute treatment.

Types of acute stroke that should be treated

All disabling strokes should be considered for immediate treatment (panel). The severity of the neurological deficit in the context of a person's activities and their quality of life before stroke defines what is meant by disabling. The National Institutes of Health Stroke Scale (NIHSS) score, originally designed as a research tool to quantify the baseline clinical neurological deficit in acute stroke trials, is widely used as a clinical assessment in hospitals for neurological deficits related to stroke. However, it is a guide that does not weight deficits or disability equally and is therefore a tool to aid, but not a substitute for, the clinical judgment of stroke severity. The score can range from 0 to 42 points as a summation of criterion-based integer scores in 11 different domains of neurological function. As a clinical guide to the scale, a score of 0–5 points suggests a mild stroke, 6–15 a moderate stroke, and greater than 15 a severe stroke. Although there is no formal lower threshold, a score of more than 5 points typically warrants consideration for acute treatment with thrombolysis in almost all cases; with lesser scores, treatment should be considered in the context of a person's premorbid quality of life and activities as well as the disability resulting from acute symptoms. However, practice varies globally, with some clinicians regarding treatment of minor stroke with thrombolysis as a standard of care and others considering thrombolysis of minor stroke to be an important unresolved research question. Patients with minor stroke are at risk of subsequent deterioration and disability.[5] Establishing the balance between risk and benefit is the impetus for ongoing randomised clinical trials of thrombolysis in minor stroke.[6]

Acute treatment for ischaemic strokes aims to restore brain tissue perfusion. Restoration is achieved medically using a thrombolytic drug or by intervention with endovascular treatment, or both. Only a few of the total population of patients with ischaemic stroke are eligible for acute therapy because the stroke is either non-disabling

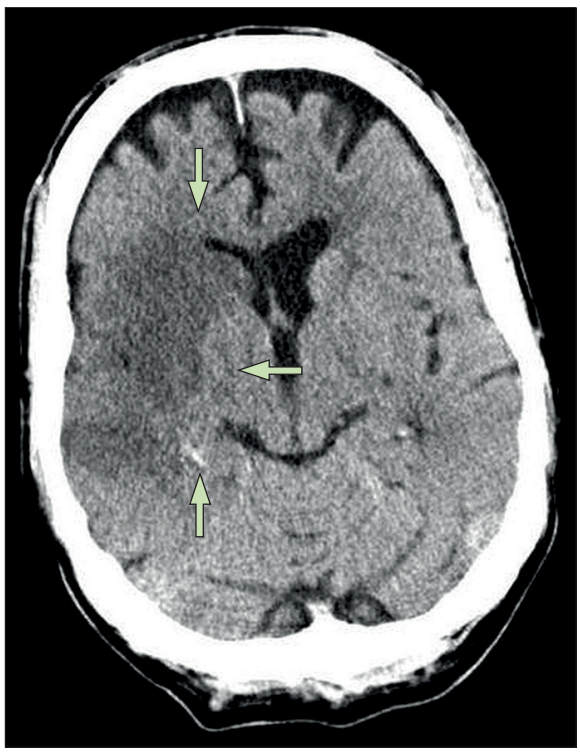

Figure 1: Non-contrast CT of a patient presenting with a right-hemispheric stroke syndrome
The scan reveals hypoattenuating brain tissue and focal swelling in the right middle cerebral artery territory consistent with an acute ischaemic stroke.

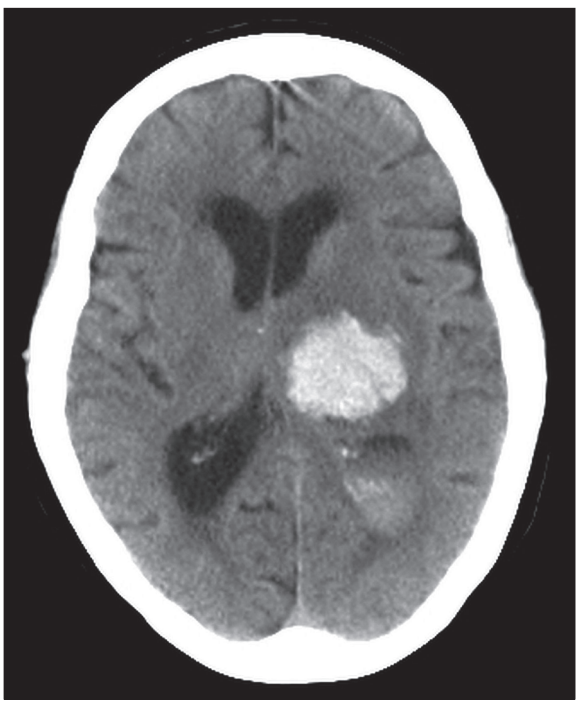

Figure 2: Non-contrast CT of a patient presenting with a hypertensive intracerebral haemorrhage originating from the left thalamus extending into the left lateral ventricle

or contraindications to thrombolysis (panel) exist. Approximately 25% of all ischaemic stroke is eligible for medical thrombolysis and 10–12% eligible for endovascular treatment. Since endovascular treatment is only applicable to large vessel occlusions, arterial imaging is necessary to define the location of the occlusion.

Imaging as the biomarker for ischaemic stroke

Unlike the analogous situation in acute coronary syndromes with high-specificity serum troponin T levels, there is no serum biomarker for acute ischaemic stroke. Known protein markers such as S100β and neuron-specific enolase levels measured at 24–72 hours correlate with infarct volume.[7] However, no single or combination of the available blood biomarkers provides differentiation of ischaemic stroke and intracerebral haemorrhage with sufficient diagnostic accuracy to guide acute stroke treatment.[8] This differentiation is only achieved by neuroimaging.

Because of its fast acquisition and widespread availability, non-contrast CT is most widely used for acute stroke syndromes. Non-contrast CT allows differentiation between ischaemic stroke and intracerebral haemorrhage and, in the case of an ischaemic stroke, allows quantification of the extent of early ischaemic changes by applying the Alberta Stroke Program Early CT Score (ASPECTS), a 10-point score that subtracts a point for each region of parenchymal hypoattenuation within the anterior circulation.[9] Scan quality, training, and experience affect the inter-rater reliability of ASPECTS but dichotomisation or trichotomisation improves reproducibility.[10] Lower scores are predictive of a poor functional outcome and similarly, lower scores are associated with an increased risk of intraparenchymal haemorrhage associated with thrombolysis.[11,12] A normal non-contrast CT does not rule out an acute ischaemic stroke; non-contrast CT has a low negative predictive value for small ischaemic volumes and therefore is commonly normal in minor or clinically resolved ischaemic stroke. Non-contrast CT can exclude alternate causes for neurological symptoms such as subdural haematoma, brain tumour, or other space-occupying lesions.

CT angiography uses iodinated radio-contrast media to image intracranial and extracranial blood vessels. CT angiography is used to identify proximal vessel occlusions as possible target lesions for endovascular treatment and should be a concurrent imaging study for patients with stroke. Neurointerventionalists can plan an endovascular procedure with CT angiography information about aortic arch tortuosity, Willisian and pial collateral status, as well as the site, characteristics, and length of the intracranial thrombus. The collateral status is estimated by comparing backfilling pial arteries in the affected hemisphere (distal to the occlusion) to the unaffected hemisphere. Poor collateral status is associated with larger volumes of irreversibly injured brain (ischaemic core)

at baseline and worse functional outcome after reperfusion therapies, independent of patient age, vessel occlusion, and time since symptom onset.[13,14] Assessment of collateral status has improved with the development of multiphase CT angiography, which generates time-resolved images of pial arteries by triggering the first scan in the late arterial phase on the basis of bolus monitoring and acquiring two subsequent scans without additional contrast in the mid-venous and late-venous phase. Multiphase CT angiography imaging is only minimally vulnerable to poor contrast-bolus timing and patient motion and the asymmetry in collateral filling can be used to help identify distal intracranial occlusions, even for inexperienced scan readers.[15]

Similarly, CT perfusion assesses collateral blood flow by repeatedly imaging the brain during transit of a rapidly administered bolus of intravenous contrast injection. CT perfusion produces maps of the total amount and delay in arrival of blood flowing through the brain vasculature and improves diagnostic confidence in differentiating ischaemic stroke from mimics (eg, a stroke will show a region of hypoperfusion and up to 50% of acute seizures will show a region of hyperperfusion). Whereas CT angiography images the larger vessels only, CT perfusion includes capillary and venular flow. Quantitative perfusion thresholds are used to estimate tissue that is already irreversibly damaged (core), tissue that is likely to infarct but salvageable with reperfusion (ischaemic penumbra), and tissue that is not threatened but might have reduced blood flow (benign oligaemia). CT perfusion thresholds that estimate ischaemic core and penumbra have been validated by comparison with follow-up infarction, defined by DWI, often done within an hour of CT perfusion, or with follow-up infarction in patients who have reperfused within 24 h after stroke onset. The predictive thresholds for these tissue states vary with imaging-to-reperfusion time.[16,17] Even brain regions with severe perfusion impairment might be salvageable with timely reperfusion and thus the predictive value of CT perfusion core estimates is imperfect. In practice with existing treatment paradigms, a severe reduction (eg, relative cerebral blood flow <30% of normal brain) has shown utility as a marker of irreversible injury in several trials, including late-window treatment trials.[18–23] Automated software now allows timely post-processing of CT perfusion functional maps that are robust to common artifacts, allowing rapid clinician interpretation.[24] However, care is required to avoid delaying treatment decisions because of the time taken to acquire, transfer, post-process, and interpret CT perfusion data.

MRI provides some diagnostic advantages compared with non-contrast CT, but in most centres takes longer to access and acquire. DWI maps show early ischaemic changes within minutes from stroke onset and a correlating apparent diffusion coefficient map visualises the extent of cytotoxic oedema caused by brain ischaemia. There is no equivalent CT technique or parameter, although regional hypoattenuation on CT is highly predictive of restricted diffusion on MRI.[25] MRI is especially useful in detecting minor strokes and differentiating ischaemic stroke from mimics in the setting of ischaemic lesions of small volume (figure 3), multiple embolic lesions, and in posterior circulation strokes where the skull base creates bony artefacts on non-contrast CT. Time-of-flight MR angiography enables a flow-dependent visualisation of the brain arteries without the need for a contrast agent. Susceptibility-weighted imaging allows for the detection of intracerebral haemorrhage with high sensitivity, and the detection of cerebral microbleeds not captured by non-contrast CT, which might indicate underlying pathophysiologies, such as cerebral amyloid angiopathy, and might be associated with an increased risk of intracranial haemorrhage after intravenous thrombolysis.[26] Specific MRI patterns of

Panel: Indication for thrombolysis

Indications

- Disabling (in the context of a person's activities and their pre-stroke quality of life) acute ischaemic stroke inpatients aged 18 years or older
- Favourable CT brain imaging (ASPECTS score of 5 or higher, no extensive regions of clear hypoattenuation)

Absolute contraindications

- CT brain imaging reveals acute intracranial haemorrhage
- Active or recent bleeding at a non-compressible site (eg, recent gastrointestinal bleed, recent intracranial or major surgery, recent major trauma)

Relative contraindications*

- Presentation more than 4·5 h from time last seen well
- Coagulopathy (platelet count less than 100 Gpt/L, international normalised ratio [INR] greater than 1·7, activated partial thromboplastin time greater than 40 s, or prothrombin time greater than 15 s)
- Blood pressure more than 185/110 mm Hg
- Current treatment with an anticoagulant (thrombin or factor Xa inhibitor, heparin, low-molecular weight heparin), unless laboratory coagulations tests results are normal (INR less than or equal to 1·7) or provide proof of normal coagulation status
- Prior intracranial haemorrhage within 3 months
- Prior ischaemic stroke within 3 months
- Systemic malignancy
- Intracranial malignant neoplasm
- Intracranial arterial dissection
- Blood glucose less than 2 mM or greater than 22 mmol/L
- Suspected or diagnosed aortic dissection
- Large (greater than 10 mm) unruptured and unsecured intracranial aneurysm
- Previous high burden of cerebral microbleeds (more than 10)
- Pregnancy

Thrombolysis indications, relative and absolute contraindications adapted from the Canadian Stroke Best Practice Recommendations: Hyperacute Care Guidelines (Update 2015),[23] 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, and European Stroke Organization Guidelines for management of ischaemic stroke and transient ischemic attack 2008.[4] ASPECTS=Alberta Stroke Program Early Computed Tomography Scale. *Relative contraindications mean that a clinical judgment must be made on the risk versus predicted benefit for treatment. For example, risk is low for patients with low or high baseline serum glucose or prior ischaemic stroke, or for those with existing intracranial unruptured aneurysms, but many trials excluded these patients from enrolment. Risk is probably somewhat higher, but not quantifiable, and the benefit less well known in patients with systemic malignancy or prior intracerebral haemorrhage or some degree of coagulopathy.

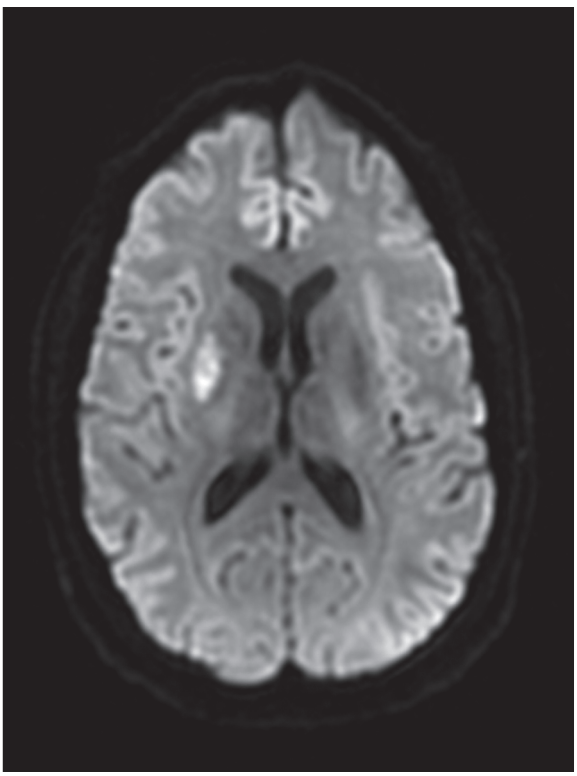

Figure 3: MRI showing an acute ischaemic stroke in the right lentiform nucleus

infarction might suggest a stroke mechanism, and, within limits, can date stroke age.[27] A mismatch between DWI and fluid-attenuated inversion recovery (FLAIR) sequence has been proposed as the criterion for the selection of patients who will benefit from thrombolytic therapy even though their time of stroke onset is unknown. In the WAKE-UP trial, intravenous thrombolysis with alteplase guided by DWI–FLAIR mismatch was effective and resulted in a significantly better functional outcome than placebo in patients with stroke of unknown symptom onset.[28] This imaging approach is used in other ongoing clinical trials to further test the efficacy and safety of intravenous thrombolysis in acute stroke syndromes with unknown time of symptom onset (NCT02002325). Contrary to usual static vascular imaging techniques, contrast-enhanced dynamic MR angiography now allows time-resolved assessment of arterial occlusions, cerebral haemodynamics, and collateral circulation in the acute setting.[29] MR perfusion imaging can use a gadolinium contrast agent and produces similar maps to CT perfusion. Arterial spin labelling perfusion imaging does not require contrast injection but the delay in endogenous tracer arrival limits measurements of cerebral blood flow within the territory affected by stroke.[30]

Imaging is the most important biomarker in acute ischaemic stroke; it can define the cause, show the extent of potentially salvageable brain tissue, and aid the selection of acute therapies. With additional imaging, time spent on imaging acquisition and processing delays treatment initiation. The threshold for when sufficient information is available to make a correct therapeutic decision should be short. Acute ischaemic stroke is a medical emergency and the average infarct progression of an untreated middle cerebral artery stroke leads to a loss of 1·9 million neurons per minute, which means that each 1 min delay of treatment is correlated with a loss of 1·8 days' healthy life.[31] The chance of poor outcome with treatment increases while time passes with each additional test obtained.[32]

Acute treatment of ischaemic stroke

Thrombolytic therapy

Open angiographic evidence of occlusions of the carotid artery and the more distal vascular tree was first documented in the late 1930s. However, early studies using fibrinolytic agents did not progress to larger randomised trials because non-invasive imaging of the brain and neurovasculature was not available until half a century later.[33] Intravenous urokinase and streptokinase did not improve clinical outcomes and, in some studies, were associated with increased risk of intracerebral haemorrhage and have since been abandoned.[34,35] Subsequently, alteplase—a single-chain recombinant tissue plasminogen activator (tPA)—has been successfully shown to be an efficacious treatment for stroke and subsequently marketed worldwide for acute ischaemic stroke treatment. The NINDS tPA stroke trial showed an increase in good outcomes at 3 months using 0·9 mg/kg intravenous alteplase compared with placebo in two parallel trials, leading to the licensing of alteplase in a 3-hour time window from stroke symptom onset.[36] The ECASS II and ATLANTIS-B trials were neutral for their chosen primary outcomes but were combined in a pooled individual patient meta-analysis including over 2000 patients treated within 360 min from stroke symptom onset.[37,38] This post-hoc analysis showed a distinct benefit of alteplase that was greater the earlier it was given, approaching a neutral effect at 270 min (4·5 h) from symptom onset.[39] The ECASS III trial verified the sustained benefit of alteplase in the 3–4·5-hour window but established that any delay in alteplase administration increased the risk of treatment-associated symptomatic intracerebral haemorrhage.[40] Thus, time from stroke onset to treatment initiation, although an unreliable surrogate marker for the extent of brain ischaemia, has been shown to be a strong effect modifier for alteplase treatment when pooling multiple large studies, showing no average benefit of alteplase administration after 270 min from stroke symptom onset.[41] IST-3, the largest thrombolysis trial, took almost a decade to complete. Although treating many patients at the periphery of present guidelines the trial showed improved functional outcome due to thrombolysis within 6 h that was even preserved in the elderly (>50% of patients were aged >80 years).[42] An updated systematic review and

meta-analysis including over 10 000 patients showed that thrombolysis given within 6 hours produced functional benefits and that those treated within the first 3 hours derived substantially more benefit than those treated later (table).[46]

The large number of patients in IST-3 allowed for multiple secondary analyses that were informative. Despite increased risk of symptomatic intracerebral haemorrhage, thrombolysis has a net clinical benefit in patients with leukoaraiosis on baseline imaging and should not be withheld on the basis of this finding alone.[47] Prespecified subgroups in IST-3 did not show differing functional outcomes but thrombolysis was associated with increased odds of symptomatic intracerebral haemorrhage among patients who had previously taken antiplatelet agents.[48] The subsequent ENCHANTED trial comparing low-dose versus standard-dose alteplase treatment in patients on prior antiplatelet therapy was neutral. However, there were fewer symptomatic intracerebral haemorrhages in the low-dose alteplase group, particularly among patients without prior antiplatelet treatment.[49] Many studies have speculated that patients on prior antiplatelet treatment are at greater risk for symptomatic intracerebral haemorrhage, partly related to the greater occurrence of vascular risk factors that warrant antiplatelet treatment. Data on the thrombolysis-associated risk of symptomatic intracerebral haemorrhage in patients with dual antiplatelet treatment are limited by the small number of outcomes.[50,51] Further randomised clinical trials are necessary to identify a subgroup of patients who would potentially benefit from low-dose alteplase treatment. Another multicentre, randomised controlled trial comparing patients who were given intravenous aspirin versus placebo within 90 min after intravenous thrombolysis treatment was stopped early because of an excess incidence of symptomatic intracerebral haemorrhage and no evidence of benefit at 3 months in the aspirin group.[52]

Alteplase has insufficient efficacy for early recanalisation in proximal vessel occlusions. Other thrombolytic agents, such as desmoteplase, showed a good safety profile within a 9-h window but failed to show efficacy in another study.[53–56] Small studies comparing tenecteplase with alteplase have shown tenecteplase to have superior fibrinolytic activity with increased rates of reperfusion.[57,58] However, the NOR-TEST trial showed that tenecteplase was not superior to alteplase in 1100 patients with acute ischaemic stroke, despite the drugs having a similar safety profile.[59] NOR-TEST has been criticised for enrolling a high number of patients with stroke mimics and treating a population of low clinical stroke severity.[60] Nevertheless, ease of use, higher reperfusion rates, and safety could result in tenecteplase replacing alteplase. The EXTEND-IA TNK trial showed that tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase among patients with ischaemic stroke treated within 4·5 h of symptom onset.[61] Three other ongoing phase 3 trials (TEMPO-2: NCT02398656; TASTE: ACTRN12613000243718; TWIST: NCT03181360) will provide further data.

	Effect on 90-day outcome (mRS 0–1)	Effect on safety (sICH within 36 h)	ARR	NNT
Thrombolysis				
0–3 h	1·75 (1·35–2·27)	6·67 (4·11–10·84)	0·098	10
3–4·5 h	1·26 (1·05–1·51)	..	0·053	19
>4·5 h	1·15 (0·95–1·40)	..	0·020	50
Endovascular treatment				
0–12 h	2·49 (1·84–3·35)	0·99 (0·60–1·63)	0·140	7

Data are OR (95% CI), unless otherwise indicated. Data are from the meta-analysis by the Stroke Thrombolysis Trialists' Collaborative Group and the HERMES collaboration.[43,44] No meta-analysis has been done to assess the effect of endovascular treatment beyond 12 h. mRS=modified Rankin Scale. sICH=symptomatic (a deterioration in National Institutes of Health Stroke Scale Score of ≥4) intracranial haemorrhage type 2 within 24 h (SITS-MOST definition[45]); OR=odds ratio. ARR=absolute risk reduction. NNT=number needed to treat to benefit one additional patient.

Table: Efficacy and safety of acute ischaemic stroke treatment

Endovascular therapy

After the exciting but preliminary results of the PROACT-2 trial in 1999 showing improved outcome for patients with proximal middle cerebral artery occlusions treated with intra-arterial pro-urokinase, subsequent trials (SYNTHESIS-EXPANSION, MR RESCUE, and IMS III) investigating the benefits of endovascular treatment for acute ischaemic stroke produced neutral results. A combination of factors, including trial design features, insufficiently clear imaging selection criteria, slow treatment process times, and the use of various older devices might have contributed to these neutral results.[62]

In 2015 and 2016, six positive trials (MR CLEAN, ESCAPE, EXTEND-IA, REVASCAT, SWIFT-PRIME, and THRACE) of endovascular treatment for large vessel occlusion of the anterior circulation established this therapy as a new standard of care. Each of these trials enrolled 70–500 previously healthy patients aged 18 years or older presenting with varying stroke severity up to 12 h from symptom onset, as well as optional additional intravenous thrombolysis treatment and extracranial occlusions.[20,21,63–66] Many of the trials emphasised speed in achieving recanalisation and thus targeted a major shortcoming of previously neutral trials. Careful imaging-based selection of the most appropriate patients, recognition of the importance of fast workflow, and the high reperfusion rates led to the overwhelming efficacy of endovascular treatment compared to standard care alone (figure 4).

The pooled, individual-patient meta-analysis showed improved functional outcome at 90 days for patients who had received endovascular treatment compared with those who had not (table).[43] Most patients in these trials were treated within 6 h from symptom onset, but even late presenters (5·5–12 h from symptom onset) in the ESCAPE trial had a treatment effect favouring endovascular

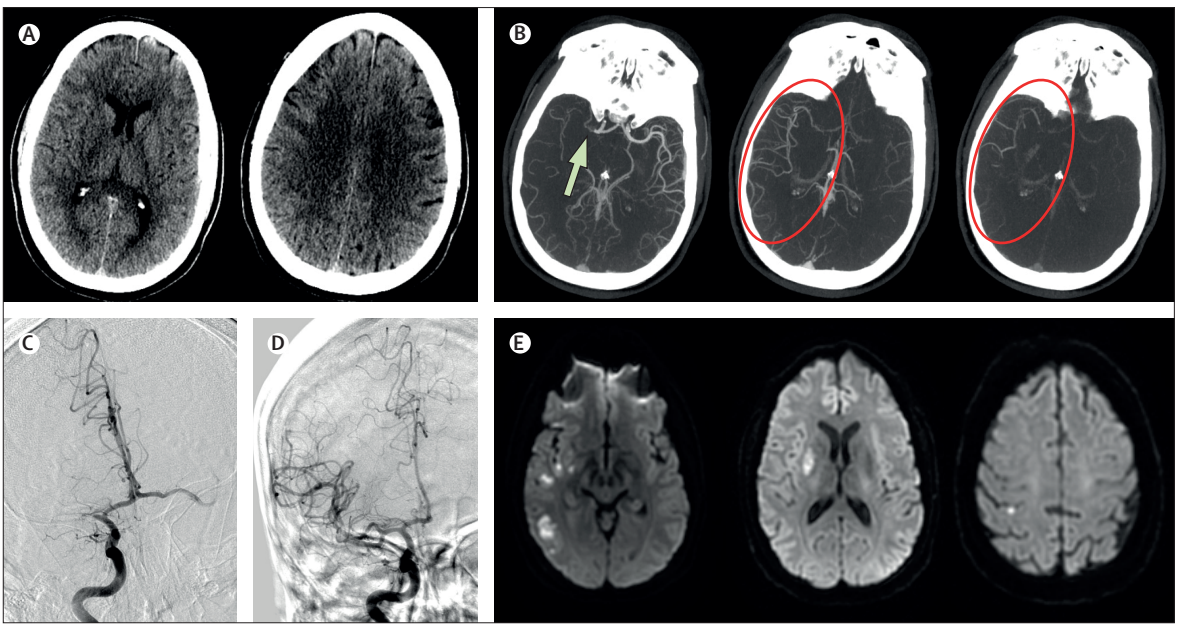

***Figure 4*: Imaging modalities used to diagnose and treat acute ischaemic stroke**
56-year-old man who was last seen normal at 2300 h. He awoke at 0500 h with left-sided weakness of the arm, leg, and face, as well as moderate dysarthria, and visual neglect (NIHSS score of 11). (A) Non-contrast CT of the head; (B) multiphase CT angiography in peak arterial, mid-venous, and late-venous phase (from left to right) showing the middle cerebral artery occlusion at the M1 segment (green arrow) and delayed arrival of the contrast agent with subsequent delayed washout in the right middle cerebral artery (red circles); (C) first intracranial angiographic run confirming a right middle cerebral artery occlusion; (D) final intracranial angiographic run post stent retrieval showing (near) complete reperfusion; (E) next day follow-up MRI showing a small volume ischaemic lesion in the right middle cerebral artery territory. Patient clinically improved to an NIHSS score of 4.

treatment across all clinical outcomes.[67] The DAWN trial showed that endovascular treatment was beneficial in highly selected patients 6–24 h after symptom onset when compared with medical treatment alone. Selection with CT perfusion MRI to identify potentially salvageable brain tissue was required.[68] The DEFUSE-3 trial, similarly requiring advanced CT perfusion or perfusion MRI for patient selection, was halted early and showed that patients receiving endovascular treatment 6–16 h after time last seen normal resulted in better functional outcomes than medical treatment.[22] These two trials emphasise the relevance of the tissue window (with imaging as the biomarker identifying salvageable brain tissue) as the physiological signature that defines a patient with treatable stroke. Patient selection with advanced neuroimaging, such as perfusion-weighted or diffusion-weighted imaging, is being further used in several ongoing trials (EXTEND: NCT01580839; POSITIVE: NCT01852201), with time windows up to 24 h from symptom onset to test the extent of treatment benefit in late presenters. Despite these late-window studies, fast delivery of treatment remains crucial; the SWIFT-PRIME trial reported that reperfusion within 150 min from symptom onset in the intervention arm led to a 91% estimated probability of functional independence, which decreased by 10% over the next hour and by 20% with every subsequent hour of delay.[69]

Stent retrieval is a common first choice of neuro-interventionalists and these devices have been used almost exclusively in clinical trials within the past 5 years. In the ASTER trial first-line contact aspiration during endovascular treatment compared with stent retrieval did not result in an increased successful revascularisation rate.[70] Previously acquired pilot data by another group using contact aspiration have shown lower procedure times and device costs compared with stent retrieval, which is why a randomised controlled trial comparing the two techniques is underway (COMPASS: NCT02466893). Other devices, like the EmboTrap device, are being investigated (ARISE II: NCT02488915).

Stroke systems of care

Since fast treatment is so important to good outcomes, organisation of stroke care is essential for timely treatment initiation. endovascular treatment can only be performed at selected capable stroke centres (usually tertiary hospitals), whereas thrombolytic treatment is available more widely at smaller hospitals. Patients identified in the field with a disabling stroke can therefore be either directly transported to an endovascular capable centre, even if that means bypassing a closer primary stroke centre (mothership model), or be transported to the nearest primary stroke centre for thrombolytic treatment first and then, if appropriate, be transferred to the endovascular capable centre (drip and ship model). Transport times and distribution of primary centres and endovascular capable centres will determine the optimal approach. Telemedicine can be

used to assist decision making for either of the models, as neurologists stationed at an endovascular capable centre can be consulted by health-care providers in primary stroke centres or even pre-hospital care providers in ambulances. Mobile stroke units are ambulances equipped with a CT scanner, a point of care laboratory, and specialised staff and allow for early diagnosis aided by neuroimaging and thus identify eligibility and even initiate thrombolytic treatment en route to the hospital.[71,72] There are ongoing efforts to develop prehospital stroke scales to differentiate large artery occlusions from other types of strokes to allow the most appropriate triage.[73] Additionally, multiple ongoing trials are assessing current transportation dilemmas, such as being taken directly to an endovascular capable centre versus directly to a primary stroke centre for patients with suspected large vessel occlusion (NCT02795962), and initiation of thrombolytic treatment on a mobile stroke unit versus in the hospital (BEST-MSU: NCT02190500; B_PROUD: NCT02869386). How patients are best advanced through the health system to have timely and appropriate access to acute stroke treatment will be an evolving standard depending on geography, infrastructure, population density, politics, and technology.

An integral part of geographical access to acute stroke care is how to optimise the workflow in each of the contributing sectors to treat patients with ischaemic stroke as quickly as possible. Systematic quality improvements can lead to much faster door-to-needle times compared with those being currently achieved, without an increase in complications. Helsinki University Hospital (Helsinki, Finland) established a high standard by lowering their median door-to-needle times to 20 min in 2011; the hospital's model was then successfully replicated at the Royal Melbourne Hospital (Melbourne, Australia) and improvements in the USA have been reported by the Target Stroke initiative.[74–76] The key to shorter door-to-needle time is a well organised stroke service, the so-called chain of recovery. Emergency call centres, paramedics, and the emergency department of the receiving hospital must work seamlessly together. Clinical assessment, imaging, and decision making for thrombolysis and endovascular treatment need to occur in parallel rather than sequentially and hospital pre-notification with transport of the patient direct to the CT scanner on the ambulance stretcher are key to achieving a revised door-to-needle time target of 30 min.[77]

All patients with acute stroke, whether it is ischaemic or haemorrhagic, benefit from stroke unit care.[78] This benefit holds true after successful reperfusion therapy. Acute stroke unit care is designed to prevent complications such as pulmonary embolism and aspiration pneumonia. Diagnostic work-up at a stroke unit makes early secondary prevention possible based on the cause of the stroke. Treatment of risk factors and evaluation of the need for rehabilitation can be initiated early at the stroke unit. Evidence-based stroke unit care will increase the likelihood of good functional outcome of stroke patients.[79]

Adjuvant and novel therapies for ischaemic stroke

Future technology to improve stroke diagnosis in the field, advances in neuroimaging, improvements in medical reperfusion therapy, advances in catheters to optimise complete reperfusion rates, and adjuvant medication to reduce permanent brain injury are all under active investigation. Importantly, improvements in catheters for stroke treatment might be influenced by regional differences in disease burden. In Asia, intracranial stenosis due to underlying intracranial atherosclerosis is a more prevalent cause of stroke than in the rest of the world.[80] Residual intracranial stenosis might require angioplasty and stenting or the use of antiplatelet infusion medication.[81] Potential improvements in medical therapy in general include sonothrombolysis and magnetically enhanced thrombolysis with iron nanoparticles (NCT03098732) and continued investigation of tenecteplase as a primary thrombolytic drug.[82]

Attempts to translate beneficial findings of high-flow oxygen and hypothermia from preclinical models to human models have been previously disappointing. Yet, adjuvant therapy for stroke is evolving. While over 1000 putative neuroprotective compounds have not been translated from the laboratory to humans, most were tested in an ischaemia-reperfusion model (temporary middle cerebral artery occlusion).[83] Human stroke due to large vessel occlusion does not commonly show early reperfusion with medical treatment, but advances in endovascular treatment have resulted in a true human ischaemia-early reperfusion model. Molecules such as the peptide NA-1 (also known as Tat-NR2B9c) are being investigated in this setting.[84] ESCAPE-NA1 (NCT02930018) is enrolling patients with large vessel occlusions about to undergo endovascular treatment to receive NA-1 or placebo. Since magnesium sulphate has been shown to be safe in the prehospital setting, a trial investigating the potential for the molecule to preserve ischaemic penumbra until the patient can undergo endovascular treatment with definite recanalisation might be considered.[85] The medical management of hyperglycaemia, hypertension, and hyperthermia or pyrexia in acute ischaemic stroke remains to be further defined. Although it is well proven that hyperglycaemia, elevated or very low blood pressure, and elevated body temperature are all associated with poor outcomes, it is not known whether intervention will actually result in better outcomes.[86–88]

Finally, innovation might occur in stroke treatment processes. Imaging with dynamic angiography equipment can allow a direct-to-angiography workflow, further reducing door-to-treatment time. As the technology for

this approach to imaging improves and becomes installed in hospitals, we expect this approach to treatment of selected patients to increasingly take place. This evolution will be accelerated if non-invasive technology plus clinical evaluation allows the reliable identification of large vessel occlusion in the pre-hospital setting.

Conclusion and future directions

The framework for acute ischaemic stroke therapeutics is fast treatment with a door-to-needle time target of 30 min or less and rapid escalation to endovascular treatment for patients with large vessel occlusion. Advanced neuroimaging, including arterial imaging, is the cornerstone for effective guidance of acute stroke treatment. Regional systems of stroke care are affected by geography, infrastructure, including financial resources, population density, politics, and technology and must be optimised to allow timely access to thrombolytic therapy and endovascular treatment. Because primary and comprehensive stroke centres must improve their workflow to achieve these target metrics, there is a substantial incentive to develop alternative thrombolytic agents that are easy to use, such as tenecteplase. With the establishment of endovascular treatment and a true human ischaemia reperfusion model, adjuvant therapies can be investigated. Acute stroke therapy is one of the most important advances in the therapeutics of neurological diseases and the future for new treatments looks promising.

Contributors

CZ wrote the first draft and produced the figures. All authors contributed critical edits and revisions to the final draft.

Declaration of interests

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