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Review Article

The Management of Acute Ischaemic Stroke – A Review and South African Perspective

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Abstract:

Reperfusion therapy in acute ischaemic stroke, namely intravenous thrombolysis and mechanical thrombectomy, have traditionally had strict time-based eligibility criteria. Recent advances in diagnostic and imaging modalities have resulted in a more dynamic view of eligibility for these therapies. The time clock concept may soon be superseded by the "tissue clock" concept, where accurate identification of the extent of the salvageable penumbra has been shown to result in favourable outcomes well beyond the traditional time limits in carefully selected patients. However in a low-middle income country like South Africa, the social, economic and geographic barriers to an effective acute stroke management service are often overwhelming. In this review we provide an update on the current evidence guiding management of acute ischaemic stroke, with a particular emphasis on the challenges faced in resource-constrained regions.

INTRODUCTION

Stroke is the second leading cause of death worldwide, after ischaemic heart disease.(1) Patients who survive are often left with significant disability, accounting for a large proportion of global disability-adjusted life years (DALYs).(1) The burden of disease disproportionately affects low-middle income countries, with stroke-related mortality and DALY rates 3–4 times higher compared to high-income countries.(1)

The preservation of life and the prevention of disability remain the two major priorities in stroke management. The historical apathy to the management of a patient with acute ischaemic stroke is slowly being replaced by a drive to the urgent identification and treatment of patients amenable to acute reperfusion therapies. This is in an attempt to salvage as much threatened cerebral tissue as possible, and consequently decreasing stroke-related mortality and morbidity. These therapies, which include intravenous thrombolysis (IVT) and mechanical thrombectomy (MT), are highly time-dependant and require each cog in the acute stroke management pathway to work seamlessly in order to produce good outcomes.

In this review we summarise the current evidence on the acute management of ischaemic stroke, with a particular emphasis on the practical implementation of reperfusion therapies in resource-constrained settings such as in South Africa.

1. General measures

An acute stroke is a severe medical emergency that requires immediate attention. Treatment strategies rely on careful review of clinical and imaging data. This evaluation must be done quickly because time is crucial.(2,3) Finding the correct balance between thorough assessment and fast decision-making can be challenging for healthcare professionals. With the advent of reperfusion therapies, a major emphasis in acute stroke management has been placed on prioritising urgent brain imaging upon arrival at hospital in order to rapidly establish suitability for IVT or MT. While there is clear merit in this approach, it must not occur at the expense of medical stability of the patient. Thus basic first aid principles of ensuring attention to the airway, breathing and circulation must always take precedence.

1.1 Glucose

The immediate bedside testing of blood glucose is imperative in all patients suspected of having acute ischaemic stroke as hypoglycaemia (and rarely hyperglycaemia) may mimic the signs of stroke. In addition, both hypo- and hyperglycaemia may result in neuronal damage and are associated with worse clinical outcomes.(4–6) The target glucose during acute stroke care varies according to different guidelines, with most recommending treating blood glucose over 10mml/L.(7,8) However, the overly tight

control of glucose with intravenous insulin has not been associated with a better clinical outcomes.(9)

There is no indication for any further blood tests in the acute work-up of ischaemic stroke, with the exception of an INR if the patient is on Warfarin at the time of stroke.(7)

1.2 Blood pressure

Elevated blood pressure immediately post ischaemic stroke may be multifactorial, including an acute sympathetic response and a compensatory mechanism to ensure adequate cerebral perfusion in borderline ischaemic regions. Evidence does not support the lowering of blood pressure in the hyperacute phase, and it may be potentially harmful.(10–12)

Indications to lower blood pressure in the hyperacute phase of ischaemic stroke are few:(7)

1. Patient is a candidate for IVT, and BP >185/110
2. Extreme hypertension (BP >220/120)
3. Acute ischaemic heart disease / heart failure
4. Aortic dissection
5. Hypertensive encephalopathy
6. Eclampsia/pre-eclampsia

When blood pressure treatment is required, cautious lowering by 15% over the first 24 hours is recommended. (7) Intravenous antihypertensive agents are generally preferred, such as labetalol or nicardipine. Medications likely to cause a rapid drop in blood pressure, such as immediate-release nifedipine, should be avoided.

1.3 Swallowing

Dysphagia and subsequent aspiration are a major cause of morbidity and mortality in patients with stroke. While it is beyond the scope of this paper to review all aspects of a swallowing assessment, it must be noted that a screening swallowing assessment must be performed before attempting to administer any emergency oral medication including stat antiplatelet therapy. If there is any doubt over the safety of swallowing, the patient must be kept nil per mouth with antiplatelet drugs administered via a nasogastric tube. Aspirin can also be administered rectally.(7)

2. Acute stroke imaging

The radiological assessment of acute stroke relies on two imaging methods: computed tomography (CT) and magnetic resonance imaging (MRI). Despite MRI being considered more advanced, it is more time-consuming, potentially leading to higher stroke-related disability. Therefore, CT remains the preferred imaging modality for acute stroke work-up.(13,14)

2.1 CT

The recommended initial imaging step for acute stroke patients is a non-contrast CT scan. It offers distinct advantages over MRI, including cost-effectiveness, 24/7 availability, swift and straightforward data acquisition, and widespread accessibility. In acute stroke, the primary purpose of a non-contrast CT is to rule out intracerebral haemorrhage. Subtle signs of hyperacute infarction on non-contrast CT may include the loss of the grey-white matter interface, a hyperdense middle cerebral artery (MCA), the "MCA dot" sign, both indicating fresh clot obstructing the vessel, and obscuration of the insular ribbon, basal ganglia and internal capsule.(15) It is crucial to bear in mind that a plain pre-contrast CT scan may appear normal to individuals without specialized training or expertise in brain imaging interpretation.(15)

The Alberta stroke program early CT score (ASPECTS), a 10-point quantitative CT scan score, is utilized in patients with ischaemic stroke to assess the extent of the infarction (Figure 1). For each affected region, one point is deducted from the baseline normal score of 10. Scores ≤7 indicate a lower functional outcome because of a large vessel occlusion (LVO).(16,17) A similar 10-point scoring system is available for posterior circulation acute ischaemic stroke.

2.2 MRI

MRI is more sensitive than CT at detecting acute ischaemia and differentiating strokes from stroke-mimics. However, it is more time-consuming (18,19) and is thus not recommended as a routine first-line investigation.(20) The MRI sequences required to evaluate whether the patient is eligible for reperfusion therapy include diffusion weighted imaging (DWI) and T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences.

While heightened DWI signal intensity can appear within the first few hours due to cytotoxic oedema, the signal intensity on T2-weighted and FLAIR does not exhibit changes within the initial 4.5 hours of stroke onset.(21) This disparity between DWI and FLAIR sequences, where DWI is positive while FLAIR is negative, can help estimate the time of stroke onset. It is most valuable in identifying patients who may benefit from IVT despite the time of their symptom-onset being unknown, including those with so-called "wake-up stroke".(22–24)

CT is as effective as MRI in terms of accurately detecting acute haemorrhage, thus a non-contrast CT scan remains the preferable method of excluding intracerebral haemorrhage.(25,26)

2.3 CT Angiography

CT Angiography (CTA) is the preferred immediate imaging modality for visualizing blood vessels supplying the brain. A head and neck CTA, spanning from the aortic arch to the vertex, is recommended in patients with suspected large vessel occlusion to capture all extracranial and intracranial arteries.(27) CTA serves to identifying thrombi in large proximal intracranial arteries (which may benefit from acute endovascular treatment), and determining the

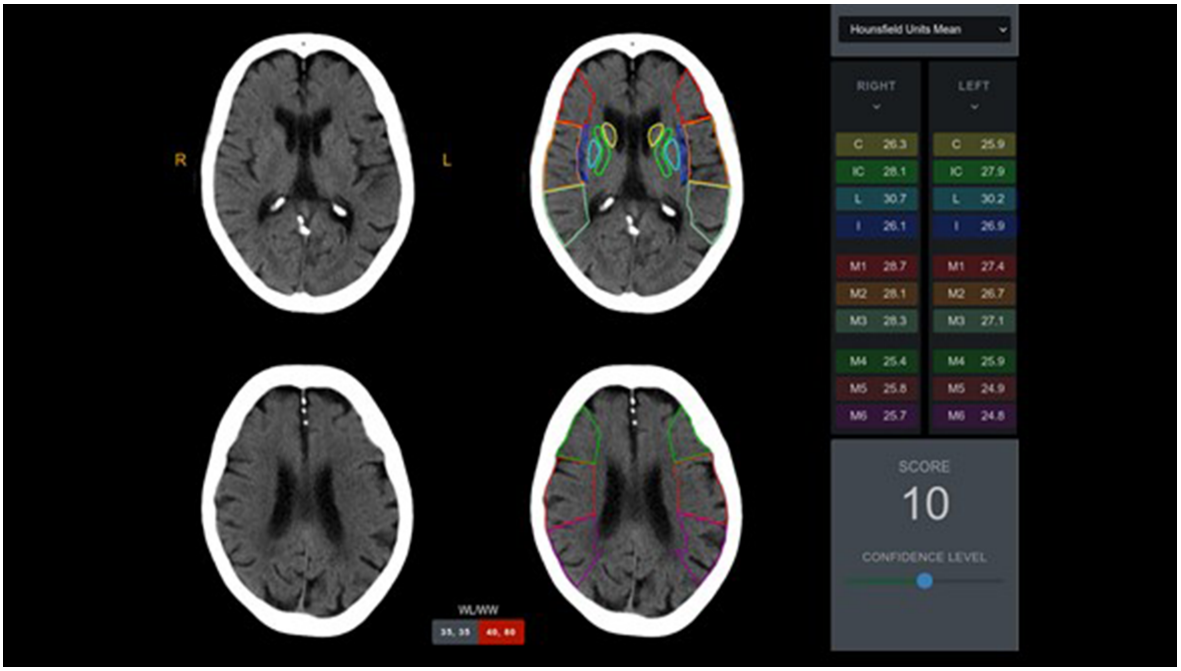


Figure 1. A non-contrast CT scan is taken at two brain levels: the ganglionic level (C = caudate head, IC = internal capsule, L = lentiform nucleus, I = insula, and M1 to M3 regions) and supraganglionic level (M4 to M6 regions).

location of thrombi within the intracranial arterial tree to assess its responsiveness to IVT (thrombi in the internal carotid artery are less likely to dissolve with IVT compared to more distal arteries).(28–30) In cases of minor strokes or transient ischaemic attacks (TIA), detecting a thrombus within the brain's arterial vasculature is of vital importance to identify patients at risk of stroke progression.(31) There is evidence to support performing CTA in every acute ischaemic stroke and this should be done immediately after the initial non-contrast CT brain without moving the patient off the CT table. It immediately alerts clinicians to LVO. It can occasionally help in making the diagnosis of stroke when there is some clinical doubt and a normal CT. It can assist in rare cases where there are mild clinical signs initially, but a LVO is present.

2.4 Perfusion studies

Advanced neuroimaging techniques, such as CT perfusion (CTP) scan, provide a valuable functional assessment of the haemodynamic state of the brain. Firstly, it aims to pinpoint the penumbra, which refers to the ischaemic, hypo-perfused tissue at risk of infarction; essentially salvageable tissue. Secondly, it seeks to identify the ischaemic core, defined as irreversibly ischaemic or infarcted tissue; the non-salvageable tissue.

CT perfusion imaging achieves these goals by combining sequential imaging with an intravascular tracer to construct high-definition perfusion maps. These maps enable the precise quantification of blood flow through different regions of the brain.(32) Subsequently, this data is transformed into perfusion maps that visually represent the hemodynamic status of specific brain tissue volumes over time. The computation of perfusion mapping hinges on the correlation between the movement of the tracer bolus through the vasculature supplying a particular brain tissue volume, as dictated by the arterial input and venous drainage phase.

The availability and utility of CTP in South Africa is presently limited to a few large centres in the public and private sector. This is largely due to software licensing costs and the lack of expertise. However, the infrastructure exists in many hospitals across the country, as most modern CT scanners can be utilised for CTP scanning.

Collectively, these imaging modalities provide a wealth of information crucial for diagnosing strokes, assessing prognosis, and guiding treatment decisions.

2.5 Acute Stroke Neuroimaging: Myths and pitfalls

2.5.1 Contrast induced Nephropathy

A meta-analysis of 14 studies (5727 patients) comparing patients who received contrast-based imaging to those who had non-contrasted imaging has shed light on the prioritization of neurons over nephrons.(33) The researchers found that brain angiography and perfusion studies do not lead to a statistically significant increase in the risk of acute kidney injury, even in patients with a known history of chronic kidney disease.(33) This data highlights the importance of promptly evaluating and diagnosing stroke

patients without undue concern for contrast-related renal complications.

2.5.2 Contrast induced anaphylaxis

It is crucial to clarify that iodine is a natural trace element found in our bodies and cannot function as an allergen. While both fish and shellfish contain iodine, it is not the iodine itself that triggers seafood allergies. Instead, the culprit is a protein known as parvalbumin and certain forms of tropomyosin found in specific seafood.(34–36) True IgE-mediated allergic anaphylaxis in response to contrast material is exceptionally rare. Therefore, concerns about iodine allergies should not hinder the timely utilization of contrast neuroimaging when indicated.(37)

3. Antiplatelet therapy in acute ischaemic stroke

The use of a stat administration of Aspirin (at a dose of 162mg to 325mg) continues to be the most widely used acute antiplatelet strategy in the setting of acute ischaemic stroke. There is longstanding high-quality evidence to support its use in this setting.(38–40)

More recent evidence strongly supports a role for the use of acute dual antiplatelet therapy (DAPT) in selected patients with acute ischaemic stroke.(41–45) Large randomised trials comparing monotherapy with aspirin to DAPT with either aspirin plus clopidogrel or aspirin plus ticagrelor all showed a lower risk of recurrent stroke at 90 days in patients on DAPT.(45–49) A meta-analysis of these trials (including over 21000 patients) reported a relative risk (RR) of recurrent stroke of 0.76 (95% CI 0.68 – 0.83) with DAPT when compared to aspirin monotherapy. There was, however, an increased risk of major bleeding events with DAPT (RR, 2.22, 95% CI 1.14–4.34).(49)

Any potential benefit of DAPT needs to be balanced against the risk of haemorrhage. Thus the use of DAPT should only be considered in patients with clinically small infarctions. In practical terms, this translates to a National Institute of Health Stroke Scale (NIHSS) score of ≤5, or a high-risk TIA with ABCD2 score of ≥4.(7,38,50,51) The ABCD2 score is described in Figure 2. The recommended duration of DAPT should not exceed 21 days. Meta-analyses of the large DAPT trials concluded that most re-strokes occur within the first 10 days, with little to no additional benefit in continuing DAPT beyond 21 days, but an increased risk of haemorrhagic complications.(45,49,52) After 21 days it is recommended to continue with a single antiplatelet agent, which is most commonly aspirin unless there is a compelling indication for an alternate antiplatelet drug.

Age	
≥60 years	1 point
< 60 years	0 points
Blood pressure (at first assessment)	
SBP≥140mmHg OR DBP≥90mmHg	1 point
SBP<140mmHg AND DBP<90mmHg	0 points
Clinical features	
Unilateral weakness	2 points
Isolated Speech Disturbance	1 point
Other	0 points
Duration of symptoms	
≥ 60 minutes	2 points
10 – 59 minutes	1 point
< 10 minutes	0 points
Diabetes mellitus	
Present	1 point
Absent	0 points

Figure 2. The ABCD^2 Score to Predict Risk of Stroke following Transient Ischaemic Attack (50)

Table 1 Recommended dosages of antiplatelet agents in acute ischaemic stroke

	Aspirin	PLUS	Clopidogrel ≠ OR	Ticagrelor ≠
Loading dose	160 – 325mg		300 – 600mg	180mg
Continuation dose	50 – 100mg daily		75mg daily	90mg BD
Duration	Indefinite*		Maximum 21 days as dual therapy with aspirin**	

≠ choose one of clopidogrel or ticagrelor to use with aspirin as DAPT
*unless complications, or an indication for anticoagulation is found, or there is an indication to switch to monotherapy with an alternate antiplatelet agent.
**after 21 days it is recommended to switch to antiplatelet monotherapy due to the risk of bleeding complications outweighing any further benefit from DAPT.

Doses of the antiplatelet agents varied in the different trials, including the use of loading doses. The recommended dosage ranges thus vary accordingly, and are shown in Table 1. A recent network metanalysis comparing DAPT with aspirin plus clopidogrel to DAPT with aspirin plus ticagrelor showed no significant difference in stroke recurrence, death and major haemorrhagic complications.(52) While ticagrelor is available in South Africa, it is not on the Essential Medicines List, and is over five-fold more expensive than clopidogrel. Thus the increased availability and lower cost of clopidogrel in South Africa will likely favour its use in the immediate future.

4. Anticoagulation in the acute setting

In patients with a newly diagnosed or known cardioembolic source for stroke, the immediate initiation or continuation of anticoagulation should only be considered if the risk of haemorrhagic conversion is extremely low, as in the case of a transient ischaemic attack (TIA). For established infarcts, most guidelines recommend deferring the initiation or continuation of anticoagulation for 4–14 days, depending on infarct size and consequent risk of haemorrhagic transformation.(7,53) (See algorithm 1) Single antiplatelet therapy may be used as bridging therapy in the interim.(7) Although clear evidence and consensus are lacking, there are certain high-risk cardioembolic scenarios (thrombus associated with mechanical heart valve or the visualisation of thrombus in the left ventricle on echocardiography) where an earlier initiation of anticoagulation may need to be considered.(54) Such uncertainties in the literature emphasize that the decision on the timing of anticoagulation initiation post-stroke should always be individualised to the patient, based on their risk of haemorrhagic transformation compared to risk of re-infarction.

The use of fractionated low molecular weight heparin for the prevention of venous thromboembolic disease is indicated in the acute ischaemic stroke setting for immobile stroke patients. The evidence for intermittent pneumatic calf compression is stronger, and is thus preferred, where available. There is no role for elastic compression stockings.(7,54)

5. Intravenous thrombolysis (IVT)

It is widely acknowledged that IVT is an effective treatment for acute ischaemic stroke.(55–57)

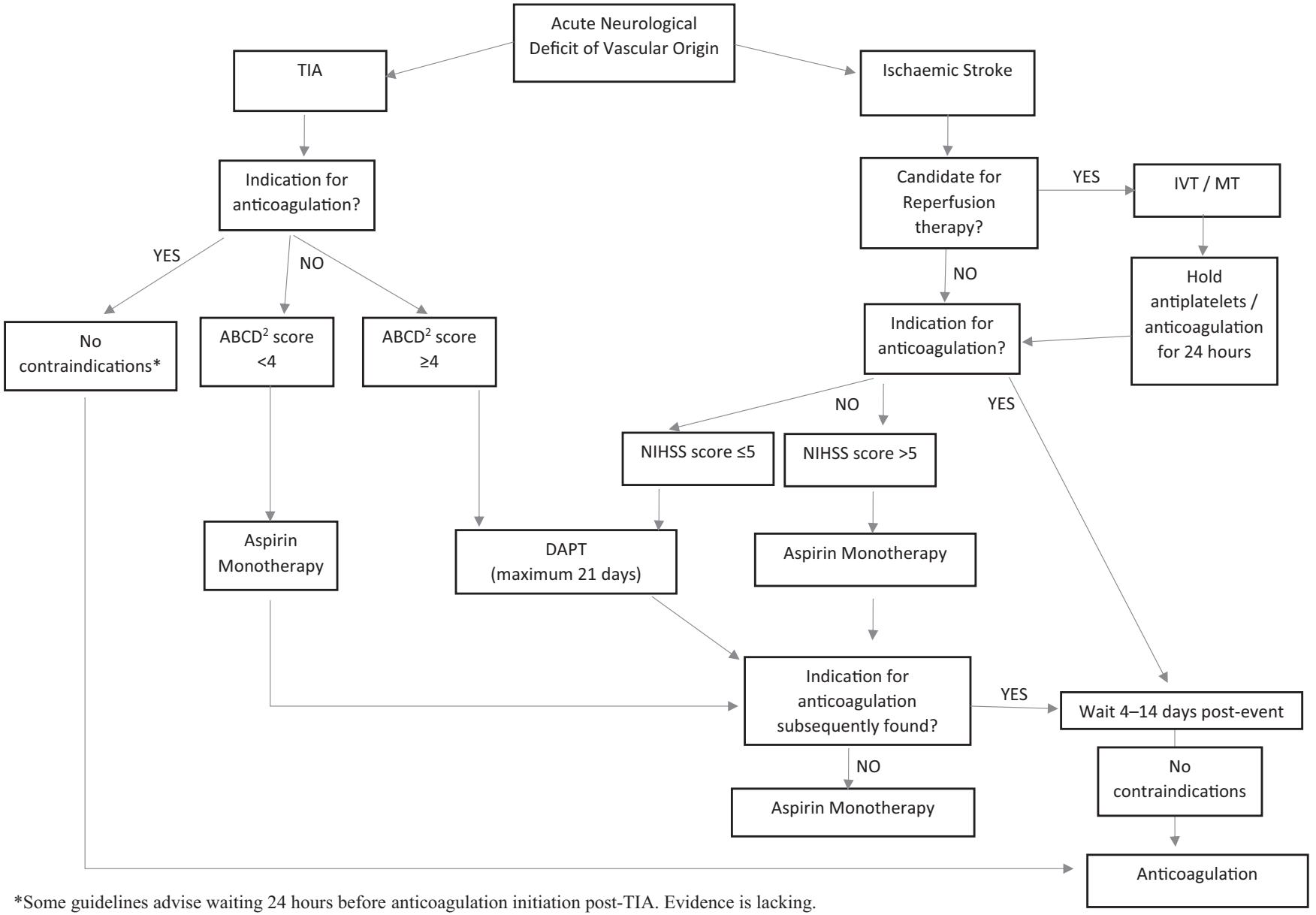
Alteplase, a second-generation tissue plasminogen activator (tPA), was initially administered in 1981 to a patient with iliac vein thrombosis.(58) Figure 3 highlights the mechanism of action of tPA. The FDA granted approval for tPA use in acute myocardial infarction in 1987.(59) Its off-label use in acute ischaemic stroke led to ECASS I, the first study to rigorously compare primary outcomes between an intention-to-treat group and a placebo control arm in patients with acute ischaemic stroke. In this study, Alteplase was administered at a dosage of 1.1 mg/kg, with a maximum dose of 100 mg and up to 6 hours from onset of stroke symptoms. However ECASS I did not find a substantial difference in major outcomes within the intention-to-treat group that received Alteplase.(60)

ECASS II followed, utilizing an adjusted Alteplase dosage of 0.9 mg/kg, capped at a maximum of 90 mg and up to 6 hours from stroke onset. Once again, the primary goals, which aimed to reintegrate patients into society with a modified ranking scale (MRS) 0 or 1, were not achieved, with an absolute risk reduction (ARR) of 3.7%. However, a post hoc analysis of ECASS II unveiled a noteworthy finding: patients in the Alteplase arm showed an ARR of 8.3% in achieving MRS 0–2, the earlier they received reperfusion therapy.(61)

The landscape of acute ischaemic stroke treatment underwent a significant transformation with the NINDS trials. Part 1, comprising 291 participants, sought to determine whether tPA exhibited clinical efficacy, assessing improvements in the National Institutes of Health Stroke Scale (NIHSS) score or resolution of neurological deficits within 24 hours of stroke onset. While Part 1 was negative, in Part 2, which included 333 participants, a global test statistic was employed to evaluate clinical outcomes at three months using various scales. Finally, the primary objective was met, demonstrating that intravenous tPA (administered at 0.9 mg/kg) within three hours of ischaemic stroke onset led to improved clinical outcomes at three months.(62)

This revelation underscored the critical principle that 'time is brain,' emphasizing the urgency of promptly treating ischaemic strokes. Each minute a LVO remains untreated results in the loss of approximately 1.9 million neurons.(57)

Further validation of the importance of timing emerged from a pooled analysis of data from the NINDS, ECASS, and ATLANTIS trials in 2002. Patients treated within



*Some guidelines advise waiting 24 hours before anticoagulation initiation post-TIA. Evidence is lacking.

Algorithm 1: The management of TIA and acute ischaemic stroke

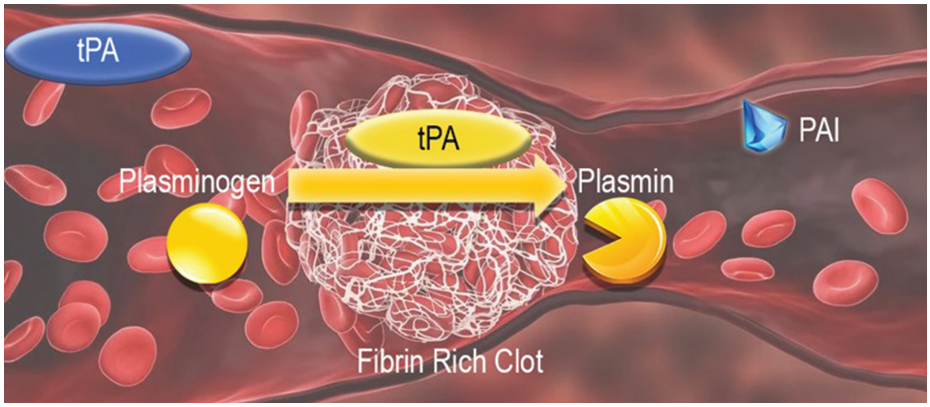


Figure 3. Alteplase binds to fibrin-rich clots, transforming plasminogen into plasmin, subsequently effectively dissolving the clot. However, in the presence of PAI (plasminogen activator inhibitor), alteplase loses its activity.

the first 90 minutes of symptom onset had nearly double the likelihood of a favourable outcome. However, statistical significance diminished after the 4.5-hour mark, potentially due to limited statistical power to detect benefits beyond this timeframe.(56,63) This combined analysis affirmed that intravenous tPA administered within three hours of stroke onset improved clinical outcomes at three months, despite a slight increase in the incidence of symptomatic intracerebral haemorrhage. Consequently, the American Heart Association (AHA) guidelines were revised to recommend tPA administration within a 3-hour window from symptom onset.(7) The therapeutic window was extended to 4.5 hours in 2008, following the ECASS III study.(64)

Furthermore, reinforcing these conclusions, a comprehensive pooled analysis of individual patient data, encompassing a substantial cohort of 2,775 individuals from six studies within the SITS-MOST registry firmly established the efficacy of intravenous alteplase, when compared to a placebo, within the treatment window of 4.5 hours after onset of acute ischaemic stroke.(64)

Current Application & Time-Window Variation (Time is Brain vs Tissue Issue)

While the critical importance of timing in administering tPA is indisputable, advancements in penumbral imaging techniques using MRI, CT perfusion and positron emission tomography (PET) have shed light on the fascinating aspect of stroke progression.(65–67) These imaging techniques have unveiled that certain patients experience a slower progression of their ischaemic stroke. As a result, this delayed progression permits the preservation of penumbral regions for an extended duration. Consequently, some individuals may still have a significant amount of penumbra even in the later stages of stroke onset (slow stroke progressors). This delay in stroke progression may result from increased collateral flow or other less apparent cytoprotective factors.(68,69) In contrast, others may experience an early conversion of penumbra into core, thus potentially eliminating the benefit of reperfusion therapy (fast stroke progressors).

Consequently, the concept of the "tissue clock" has gained prominence. This dynamic concept recognizes that the tissue clock is unique to each patient and becomes increasingly significant the longer it has been since the patient was last known to be well. By employing MRI or CTP methods, the tissue clock can be assessed for each patient, revealing the ratio of penumbral tissue volume to irreversibly damaged ischaemic core volume. This personalized approach allows for more precise and tailored decision-making in stroke treatment strategies.(70,71) It is particularly applicable in patients who have surpassed the 4.5-hour time window, or have an unknown time of symptom-onset like in wake-up strokes.(64,72,73)

Recent findings from the EXTEND-IA, DAWN, and DEFUSE 3 trials have provided compelling evidence for the efficacy of tPA in patients who awaken with stroke symptoms or have an uncertain time of symptom onset, extending the treatment window to an impressive 9 hours from the last known well state.(22,71,74) However, it is crucial to note that this extended benefit is subject to an important condition: selecting the patients based on the absence of substantial and irreversible ischaemic damage, as identified through advanced neuroimaging techniques.

Three distinct approaches have been devised to identify and assess the concept of the "tissue clock":

- *CT Perfusion Criteria-Based Core-Penumbra Mismatch* (Figure 4): This approach relies on specific criteria within CT perfusion imaging to delineate between the ischaemic core and penumbral areas. By pinpointing regions where blood supply is compromised but tissue viability persists, this method enables the quantification of salvageable brain tissue.(75)

- *Clinical Core Mismatch*: Another approach entails evaluating the core using perfusion CT or diffusion-weighted imaging (DWI) on MRI. When a patient presents with a relatively severe clinical deficit that clearly exceeds what is observable on imaging, clinicians estimate the extent of the penumbra. This estimation is grounded in the rationale that the severity of the clinical deficit is indicative of the penumbral tissue.(76)
- *DWI/FLAIR Mismatch on MRI:* This method entails assessing the DWI/FLAIR mismatch on MRI scans. This approach capitalizes on disparities between these two MRI sequences to estimate the penumbra region. While DWI highlights acute ischaemic lesions, FLAIR imaging accentuates established lesions. Discrepancies between the two sequences can signal the presence of salvageable tissue.(22,77,78)

These diverse theories and approaches have found practical utility in clinical studies involving IVT. For instance, both the EXTEND-IA and DEFUSE 3 trials effectively employed the core-penumbra mismatch concept as a guiding principle for reperfusion therapy with IVT.(71,75) Additionally, the WAKE-UP trial employed IVT based on the MRI DWI/FLAIR mismatch.(22)

Currently, the focal point of stroke management lies in tailoring treatment strategies based on visible mismatch tissue observed in advanced neuroimaging (Tissue-Issue) for optimizing stroke therapy. In clinical practice, all these diagnostic approaches have demonstrated remarkable success in guiding stroke treatment decisions.

6. Mechanical thrombectomy (MT)

A growing number of trials and meta-analyses have unequivocally proven that MT is a powerful treatment modality for LVO when compared to the best medical therapy, including IVT.(79–85) This is, provided that certain key patient, timing and imaging conditions have been met. Leading international stroke organisations have rapidly adopted these guidelines as standard of care in countries that have the necessary infrastructure and clinician skills.(7,86–88)

The HERMES collaboration (74) pooled the individual patient data from five landmark studies MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA.(80,82–85,89) These included patients with ischaemic strokes with occlusion of the carotid or middle cerebral artery (i.e. LVO) presenting within 6 hours of symptom onset. Patients had to be symptomatic with a NIHSS score of ≥6, and minimal signs of established infarction present on imaging, with an ASPECTS score >6. Data for the 1 287 patients were pooled and analysed for outcomes relating to disability, haemorrhage rate and mortality at 90 days. The individual trials, and the meta-analysis demonstrated significantly decreased disability (adjusted cOR 2·49, 95% CI 1.76–3.53; p<0.001) with numbers needed to treat (NNT) of 2.6 for one patient to improve one level on the modified Rankin Scale. There was no difference in mortality rates, nor in haemorrhage rates. These results were positive independent of the device or the imaging modality

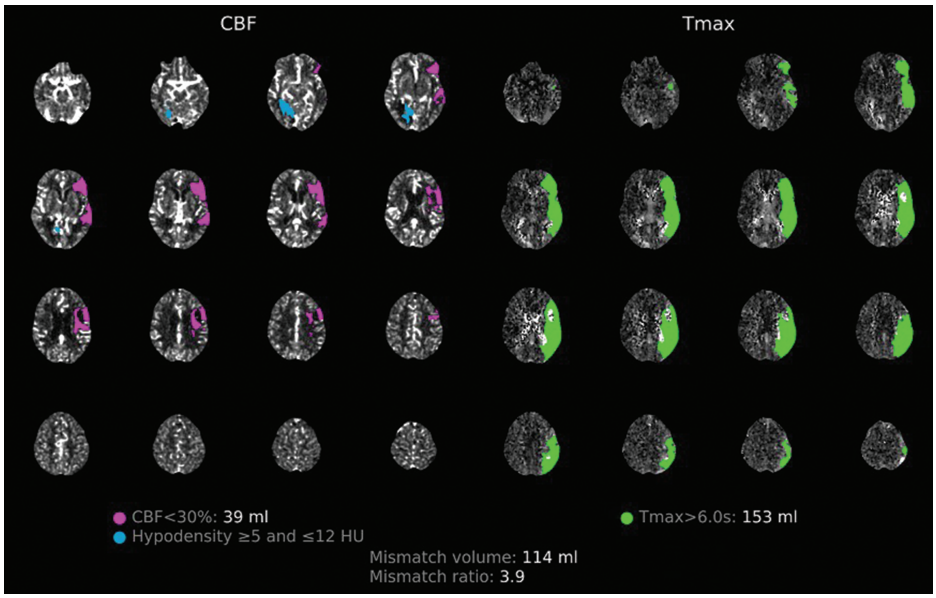
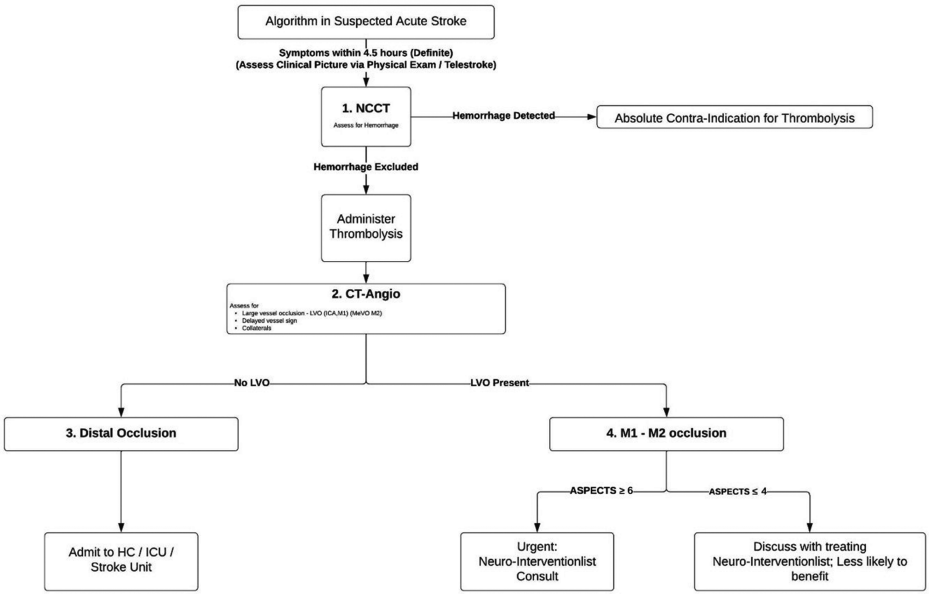


Figure 4. CT-Perfusion mismatch maps serve a pivotal role in distinguishing between irreversibly damaged tissue, depicted in pink, and regions with critically low perfusion, denoted in green.
The green areas outline the extent of the impending infarction, thereby defining the overall stroke size.
Pink regions exhibit reduced cerebral blood flow of 30% or less representing the irreversibly injured core tissue.
The "Mismatch Volume" precisely pinpoints the salvageable tissue, known as the penumbra.



Algorithm 2: Utility of CT/CT angiography

Legend to Algorithm 2:

Non-Contrast CT (NCCT) primarily serves as a diagnostic tool for the evaluation of acute intracranial haemorrhages.

Once a haemorrhage has been excluded thrombolysis is administered

CT Angiography (CTA) plays a pivotal role in identifying large vessel occlusions (LVO) in the proximal arteries, such as M1 and M2 segments.

Patients with an identifiable Large Vessel Occlusion should be discussed with the Neuro-Interventionalist

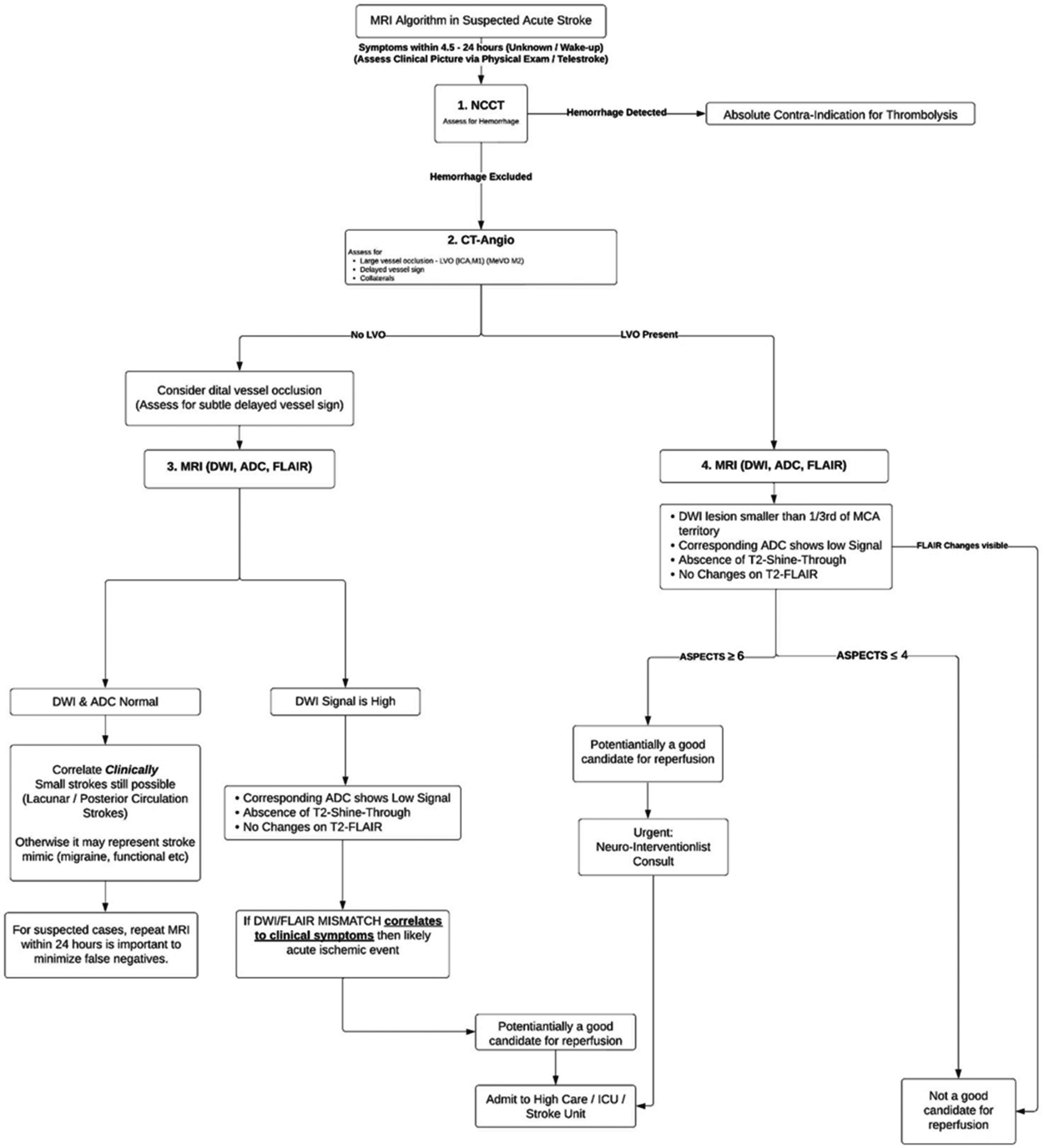
used. The primary trials typically included patients up to 6 hours from stroke onset, with some including patients up to 12 hours after onset.(80,82–85,89) Algorithm 2 summarizes the role of CT and CT angiography for the management of hyperacute stroke.

After these initial trials the research community rapidly explored extending the time frames using advanced imaging techniques. The DEFUSE-3 (77) and DAWN (78) trials utilised advanced imaging in the form of perfusion studies, or DWI-FLAIR mismatch to carefully select patients up to 16 and 24 hours after stroke onset respectively. In a similar manner to the meta-analysis of the HERMES collaboration, the AURORA collaboration included patients for MT where the stroke had occurred >6 hours prior to the intervention.(90) Pooled analysis yielded an adjusted odds ratio of 2.54 (95% CI 1.83–3.54; p<0.0001). This translates to 45.9% of patients achieving no, or mild disability in the intervention arm, compared to 19.3% of patients receiving best medical therapy, without any increase in mortality or symptomatic haemorrhages.(90) These highly selected patients had even better outcomes than those reported in the HERMES collaboration, with a NNT of 2.0 for any reduction in disability, and a NNT of 2.6 for no or mild disability (MRS of 0–1). These strikingly low NNTs are unparalleled in stroke medicine where the major IVT trials had overall NNTs of 8–14.(91) While direct comparison is difficult, the equivalent of MT in cardiology (coronary angioplasty) when compared to thrombolytics in acute myocardial infarction has a NNT of 50 to prevent death. (91,92)

As is the case with IVT, the advent of advanced brain imaging and evidence for extended time frames for MT may lead to the traditional time-based criteria being superseded by so-called "tissue-based" windows. Algorithm 3 summarizes the role of MRI in the assessment of "tissue based" windows of therapy for management of acute stroke.

With these excellent results, clinicians experienced difficulties with regards to the best method to implement these findings. Limitations in access to specialist hospitals with interventional radiology suites became apparent. This led to two main options when designing the MT service in a health district: the 'Hub-and-Spoke' model where ischaemic strokes were initially managed by peripheral hospitals (including IVT where indicated), and subsequently referred to a larger comprehensive stroke centre for MT, or the 'Mothership' model, where all patients are directly referred to the comprehensive stroke centre in order to minimise delays.(93)

In South Africa, the need to establish capable centres that can efficiently and comprehensively treat ischaemic strokes is a major challenge in optimising care for patients with stroke. The shortage of skilled interventionalists (radiologist, neurosurgeon, neurologist or cardiologist) and interventional suites, and the costs of the stent retrievers



Algorithm 3: Utility of MRI

Legend to Algorithm 3:

1. Non-Contrast CT (NCCT) primarily serves as a diagnostic tool for the evaluation of acute intracranial haemorrhages.
2. CT Angiography (CTA) plays a pivotal role in identifying large vessel occlusions (LVO) in the proximal arteries, such as M1 and M2 segments of the middle cerebral artery
3. MRI is valuable for uncertain diagnoses or symptoms beyond 4.5 hours from last known well if a potential thrombolysis candidate exhibits a DWI lesion <1/3 MCA territory with no FLAIR signal changes.

and various catheters, are major stumbling blocks both within the public and the private healthcare sectors. These difficulties are more apparent when dealing with rural communities where access to even basic healthcare facilities may be many hundreds of kilometres away from the patient.

These barriers to implementing an effective service are daunting at first glance, but are not too dissimilar to those faced in the era of interventional cardiology a few years prior. Additionally, other developing countries with limited resources are availing themselves to the challenge of establishing suitable MT services with very similar outcomes to the original trials.(94–96) Undoubtedly MT offers a powerful tool for selected patients with an ischaemic stroke due to large vessel occlusion. An effective nationally coordinated MT service needs to prioritise the training of clinicians, the creation of teams within specific hospitals, as well as co-operation to establish networks within regions to facilitate rapid transfer of suitable patients to comprehensive stroke centres.

7. Access to Acute Stroke Care in South Africa

South Africa, a country marked by a dual healthcare system comprising both public and private sectors, exemplifies the disparities in stroke care that exists within a single nation. Assessment of the socioeconomic discrepancies within a country revealed that South Africa has the highest Gini coefficient, representing the world's most unequal society.(97)

Discrepancies in stroke care between public and private healthcare systems in South Africa are a complex and multifaceted issue. Economic, geographic, and resource disparities contribute to unequal access to timeous and effective stroke care, resulting in disparate outcomes for South Africans. Addressing these disparities requires a multipronged approach involving policy reforms, increased access to healthcare services, telemedicine solutions, and public awareness campaigns.

While there are only a handful of articles on the differences between public and private health care for patients with stroke specifically,(98–101) a number of research sources point to a two-tiered health care system with massive differences in terms of ease of access, ambulance services, waiting times, access to brain imaging, medication and access to specialists.(97) Public healthcare facilities face a shortage of healthcare professionals, including neurologists and stroke specialists. In contrast, private healthcare can attract and retain specialised staff. Public healthcare facilities often lack the advanced diagnostic equipment available in private settings. This results in delayed or incomplete diagnostic workups and a limited range of treatment options, reducing the chances of optimal stroke care. This disparity in expertise and resources directly impacts the quality of stroke care provided. However a number of academic state hospitals have successfully implemented stroke units that facilitate the care of patients with stroke in the hyperacute, acute and subacute time frames. This includes the availability of MT services in a number of large state hospitals in major centres.(102,103) The shared physical environment and lack of economic competition within the state facilities can often streamline the creation of an effective team to deliver world class services.(104) Within the public healthcare system, funding allocation is based on the provincial population size. This promotes inequality as previously disadvantaged hospitals and healthcare facilities are not provided with suitable financial resources to catch up with provinces with already well-established healthcare systems. This further disadvantages patients in rural areas as they cannot easily access services that may be available in more urban provinces.(95,97,99) This is of particular concern as it relates to the use of IVT and MT with the potential to ameliorate the effects of an ischaemic stroke if accessed timeously. Rural areas often lack the necessary infrastructure, medical expertise, and diagnostic tools required for prompt stroke diagnosis and treatment, leading to delayed care and poorer outcomes. Thus, economic disparities are further compounded by geographic disparities. Telemedicine can bridge the gap between urban and rural areas by connecting remote healthcare facilities with stroke specialists in larger centres. Implementing telestroke programs can facilitate rapid diagnosis and treatment, especially in regions lacking access to specialized stroke care.(105)

Raising public awareness about stroke risk factors, prevention, and the importance of seeking immediate medical attention can also help reduce disparities. Targeted educational campaigns can empower individuals to recognize the signs of stroke and seek care promptly, regardless of their healthcare setting.

As South Africa continues to grapple with the burden of stroke, it is imperative that government, healthcare providers, and civil society work together to ensure that stroke care is equitable and accessible to all citizens, regardless of their economic or geographic circumstances. By taking concerted action, South Africa can make significant strides in reducing the disparities in stroke care and improve the overall health and well-being of its population.

CONCLUSION

Acute ischaemic stroke management continues to centre on re-establishing perfusion to a potentially salvageable penumbra of tissue around the infarcted core. Immediate administration of aspirin, intravenous thrombolysis, and mechanical thrombectomy for large vessel occlusion are proven, evidence based powerful tools to achieving this goal. Recent evidence now strongly supports the use of DAPT in selected patients for a short period. Standard imaging required for correct management decisions to be made is non-contract CT followed immediately by CT angiography. Advanced imaging techniques have demonstrated that ischaemic penumbra tissue may remain viable well beyond the traditional time limits for reperfusion therapy. The growing body of evidence demonstrating good outcomes in such patients points to the "tissue window" possibly superseding traditional time-based criteria in the near future. However, for the majority of South Africans,

access to even basic acute stroke services is limited due to economic, social and geographic barriers. Recent success stories from several centres in the public and private health sectors, demonstrate that despite disparate systems and often limited resources, acute stroke care can be provided at the level of current best practice recommendations.

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