

***How to do it: Diagnosis and management of acute ischaemic stroke***

Robert Hurford<sup>1</sup>, Alakendu Sekhar<sup>2</sup>, Tom Hughes<sup>3</sup>, Keith Muir<sup>4\*</sup>.

<sup>1</sup>Centre for the Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK; <sup>2</sup>Department of Neurology, Walton Centre Foundation Trust, Liverpool, UK; <sup>3</sup>Department of Neurology, University Hospital of Wales, Cardiff, Wales, UK; <sup>4</sup>Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, UK.

*\*Corresponding author:*

Professor Keith W. Muir  
Institute of Neuroscience and Psychology  
University of Glasgow  
Queen Elizabeth University Hospital  
Glasgow  
G51 4TF  
UK  
Email: [keith.muir@glasgow.ac.uk](mailto:keith.muir@glasgow.ac.uk)  
Telephone: 0044(0)1414515874

Number of tables: 3

Number of figures: 3

Word count (manuscript text): 3,828

**Abstract**

Acute ischaemic stroke is a major public health priority and will become increasingly relevant to neurologists of the future. The cornerstone of effective stroke care continues to be timely reperfusion treatment. This requires early recognition of symptoms by the public and first-responders, triage to an appropriate stroke centre and efficient assessment and investigation by the attending stroke team. The aim of treatment is to achieve recanalisation and reperfusion of the ischaemic penumbra with intravenous thrombolysis and/or endovascular thrombectomy in appropriately selected patients. All patients should be admitted directly to an acute stroke unit for close monitoring for early neurological deterioration and prevention of secondary complications. Prompt investigation of the mechanism of stroke allows appropriate secondary preventative treatment to be initiated. Future objectives include improving accessibility to endovascular thrombectomy, using advanced imaging to extend therapeutic windows and the development of neuroprotective agents to prevent secondary neuronal damage.

## Key Points

- Stroke is a public health priority and prompt specialist intervention significantly reduces the burden of death and disability.
- Effective systems need to be in place for pre-hospital recognition and appropriate triage of suspected acute stroke.
- Patients with non-disabling stroke or TIA should be assessed within 24 hours.
- Reperfusion with intravenous thrombolysis and/or endovascular thrombectomy are highly effective, but time-dependent, therapies.
- All patients should be treated in an acute stroke unit, monitored to detect and act on physiological insults including brain oedema, and undergo prompt aetiological investigation to allow initiation of mechanism-appropriate secondary preventative therapies

## Further Reading

- 'Transient Ischemic Attack and Stroke, Diagnosis, Investigation and Treatment', Gary KK Lau, Sarah T Pendlebury, Peter M Rothwell, 2<sup>nd</sup> Edition, Cambridge Medicine.
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## Introduction

Stroke is the fourth leading cause of death and the largest cause of adult neurological disability in the UK.<sup>1,2</sup> The associated socioeconomic burden is huge; the aggregate cost of stroke, including long-term healthcare, rehabilitation and loss of employment is estimated to be £25.6 billion per year.<sup>3</sup> As such, it is one of the key diseases targeted by the NHS Long Term Plan in England and Wales.<sup>4</sup>

In contrast to most other countries around the world, stroke medicine in the UK is not the sole preserve of neurologists, indeed most NHS stroke consultants are geriatricians. Whilst it is indisputable that stroke medicine is multidisciplinary, appropriately trained neurologists are well placed to manage stroke and its mimics. In the UK, the new neurology training curriculum will produce consultants trained in stroke medicine, which has the potential to expand the stroke workforce.<sup>4</sup> Here, we review the diagnosis and management of acute ischaemic stroke and TIA for the practising neurologist.

## Service design

The introduction of intravenous thrombolysis with recombinant tissue-type plasminogen activator (rtPA, alteplase) for treatment of acute ischaemic stroke required a revolution in the organisation of stroke care. Recognition that '*time is brain*' drove effective public and pre-hospital awareness campaigns, such as the '*Face, Arm, Speech, Time*' (FAST) test<sup>5</sup> and rapid pre-hospital triage to designated centres.

The organisation of stroke care is dependent upon local geography, but implementation of dedicated acute stroke pathways in the UK varies widely. Comprehensive Stroke Centres (CSC) provide all aspects of acute stroke care. Triage of endovascular thrombectomy (EVT)-eligible patients directly to a CSC (the 'mothership' model) even if other hospitals are closer may improve the likelihood of good outcome. Primary Stroke Centres (PSC) are usually smaller centres that initiate intravenous thrombolysis and transfer EVT-eligible patients to a CSC, the so-called 'drip and ship' model.<sup>6</sup> Rural hospitals without a stroke team can be linked with stroke centres by telemedicine for thrombolysis calls.<sup>7,8</sup> The key aspect of any stroke service model is that patients can access specialist expertise, neuroimaging and stroke unit care without delay.<sup>9</sup>

The distinction between TIA and stroke cannot be made whilst the patient remains symptomatic, and therefore all patients should be assessed rapidly. Patients with a completed TIA (symptom resolution within 24 hours) or minor, non-disabling, stroke require prompt mechanistic investigation and secondary preventative treatment, with expert review within 24 hours recommended for all suspected cases.<sup>10</sup> Organisational models to achieve

this commonly include rapid-access clinics (*Figure 1*). The remainder of this article will focus on the assessment and treatment of acute disabling ischaemic stroke.

## Diagnosis

### *Initial history*

As with all aspects of neurology, the history is a crucial diagnostic tool. However, in the acute stroke setting details need to be acquired efficiently and focussed on answering a few key questions. Collateral history from witnesses or family members is crucial as the nature of the deficit commonly precludes reliable history from the patient themselves.

*‘When was the patient last seen to be well?’* Early determination of whether the patient is within the reperfusion therapy treatment window sets the pace of subsequent investigations and aids the triage of simultaneous referrals. Symptom onset should be documented as a clock time to avoid confusion. The time recorded for unwitnessed events or ‘wake-up’ strokes should be when the patient was definitely last well (rather than when found); the surrogate use of an activity can be useful, for example waking to go to the toilet or successful use of a mobile phone.

*‘How quickly did the symptoms develop?’* Stroke symptom onset is usually sudden, although notable exceptions include the stuttering nature of capsular warning syndrome, or prodromal symptoms of basilar artery occlusion. Fluctuating severity is common in the early hours, and initial improvement may be followed by deterioration, especially among those with intracranial vessel occlusion. More gradual evolution of symptoms may suggest alternative diagnoses.

*‘Is there any significant past medical and drug history?’* A brief overview of the patient’s background, especially vascular risk factors, will influence the diagnostic decision process and can sometimes be obtained via electronic medical records before the patient’s arrival. Risk factors associated with ischaemic stroke include cigarette smoking, hypertension, hypercholesterolaemia, diabetes mellitus, cardiac or peripheral vascular disease and drugs of abuse. A history of carotid stenosis or atrial fibrillation may suggest an aetiology.<sup>11</sup> Reviewing the medication list assists screening for known relevant diagnoses, risk factors, and oral anti-coagulation therapy as a potential contraindication to thrombolysis.

Stroke mimics account for at least 20-25% of acute presentations and many of them can be suspected from the history. In one study, the five most frequent stroke mimics were seizure, syncope, sepsis, migraine and brain tumours;<sup>12</sup> detailed reviews can be found in *Practical Neurology*.<sup>13,14</sup>

Posterior circulation strokes are misdiagnosed three times more often than anterior circulation strokes, as they frequently present with non-specific symptoms, including isolated “dizziness” (vertigo or disequilibrium) or headache.<sup>15</sup> Acute onset vertigo or disequilibrium with an additional posterior circulation symptom should necessitate further assessment.

### *Examination*

An overview of the patient can be made immediately and should focus on the level of consciousness, head/ gaze deviation and laterality of purposeful movements. As in any emergency situation, an initial screen of the airway, breathing and circulation (ABC’s) and vital signs will establish cardiovascular stability and suitability to go to scan.

Up to 80% of acute ischaemic stroke patients will have elevated blood pressure ( $\geq 140$ mmHg systolic),<sup>16</sup> which spontaneously improves over the following week<sup>17–19</sup> and is associated with poorer outcomes in both ischaemic stroke and intracerebral haemorrhage (ICH).<sup>20,21</sup> The cause of transient post-stroke hypertension is unknown but potential mechanisms include disturbed cerebral autoregulation or non-stroke causes such as urinary retention or psychological stress.<sup>22</sup> Pyrexia is also common and could represent aspiration pneumonia, urinary tract infection or infective endocarditis.<sup>23</sup>

A focussed, rather than extensive, neurological examination should be performed in order to identify the affected vascular territory and quantify physical impairment using the National Institutes of Health Stroke Scale (NIHSS). Limitations to clinical examination in the hyperacute setting include the immaturity of physical signs (such as hypertonia or brisk reflexes) and the degree of patient cooperation. In agitated or dysphasic patients, there is a greater reliance on careful observation when assessing limb paresis, eye movements or visual fields.

The NIHSS is the most commonly used neurological deficit rating scale with a maximum score of 42 (hypothetical due to several mutually exclusive items). Its advantages include an accredited training and certification system (<http://www.nihstrokescale.org/>), quick completion time ( $\leq 10$  minutes<sup>24</sup>) and facilitation of communication between team members; it may be used to monitor deficit severity, identify neurological deterioration, and to select patients for reperfusion therapy. Limitations of the NIHSS include the underrepresentation of non-dominant hemisphere deficits,<sup>25</sup> such as apraxia or anosognosia which may be subtle but are potentially significantly disabling, and low sensitivity for posterior circulation deficits.<sup>26</sup>

Quick recognition of common stroke syndromes increases diagnostic confidence and facilitates an efficient neurological examination. Although of limited utility in the hyperacute setting, stroke syndromes can often be suggestive of the underlying aetiology. Large-vessel

stroke syndromes (*Table 1*) suggest atheroembolic aetiology whereas lacunar syndromes, classically associated with cerebral small-vessel disease, include contralateral pure motor, pure sensory and sensorimotor impairment, the clumsy-hand-dysarthria syndrome (which can also be cortical) and ataxic hemiparesis.

The three-step “HINTS” (Head-Impulse-Nystagmus-Test-of-Skew) bedside examination is often used to assess patients presenting with acute vestibular syndromes and is reported to have high sensitivity (100%) and specificity (96%) for detecting a central cause.<sup>27,28</sup>

However, with a positive predictive value of only 69%, an isolated abnormal head impulse test (suggestive of unilateral peripheral vestibulopathy) should be interpreted with caution.<sup>29</sup>

### *Investigations*

#### Pre-imaging

Rapid neuroimaging is essential for acute stroke patients and American Stroke Association guidelines advise that a capillary blood glucose is the only necessary prior investigation.<sup>30</sup> In practice, this is obtained by paramedics and an intravenous cannula is often required for contrast or perfusion imaging sequences, in which case a blood panel can be obtained simultaneously. This would usually include a screen for infection, renal function and, if the patient is taking anti-coagulants, a coagulation screen. Although many radiology departments require a recent renal function before giving contrast,<sup>31</sup> recent studies have brought the concept of contrast-induced nephropathy into question.<sup>32,33</sup>

#### Imaging

Stroke centres should establish protocols to eliminate delays to neuroimaging, for example protocolled stroke imaging sequences and priority use of a designated scanner in close proximity to the emergency department.

Neuroimaging in the hyperacute acute stroke setting remains predominantly CT-based<sup>34</sup> as non-contrast CT brain is quick, sensitive and cost-effective at ruling out intracranial haemorrhage, which is usually sufficient for making thrombolysis decisions.<sup>35</sup> However, CT has much lower sensitivity and specificity for acute ischaemia since net tissue water content (and therefore visual change in parenchymal attenuation) changes over hours after onset of ischaemia. Specificity is compromised by the high prevalence of existing ischaemic changes or old established infarcts. Signs of acute ischaemia on non-contrast CT include loss of grey-white matter differentiation (for example at the insular ribbon), hemispheric sulcal effacement, loss of integrity of the lentiform nucleus, or hyperdensity within an intracranial artery (the ‘dense artery sign’). Early ischaemic changes can be quantified to assess the

extent of parenchymal damage using the 10-point *Alberta Stroke Program Early CT Score* (ASPECTS).<sup>36</sup>

Multimodal CT imaging comprises CT-perfusion (CTP) and/ or CT-angiography (CTA) in addition to non-contrast CT in order to improve and broaden case selection for reperfusion therapy. Rapid multimodal CT can be performed in acute stroke care pathways. Clear protocols for efficient interpretation should be established to prevent unnecessary delays to rtPA administration.<sup>37</sup>

CTA of the cervicocranial and intracranial arteries should be performed urgently to detect intracranial large artery occlusion (LVO) when EVT is available. LVO is a marker of poor prognosis in minor stroke and TIA<sup>38</sup> and observational evidence suggests patients with non-disabling symptoms due to LVO may benefit from thrombolysis,<sup>39</sup> but a randomised trial is ongoing.<sup>40</sup>

CTP sequences are used to assess various aspects of cerebral perfusion (see discussion below), often with automated software, such as MISTar (Apollo Medical Imaging Technology) or RAPID CTP (iSchemaView), to ease interpretation by increasing inter-observer reproducibility and ensuring use of validated thresholds. A comprehensive review of CTP interpretation has recently been published in *Practical Neurology*.<sup>41</sup>

MRI has much greater sensitivity for ischaemia compared to CT, particularly in minor stroke where it is predictive of poor short and long-term outcomes.<sup>42</sup> Moreover, comparison of different sequences offers an approximate indication of time since onset.<sup>43</sup> Rapid stroke MRI protocols typically include diffusion-weighted imaging (DWI), time-of-flight MR-angiogram of the intracranial arteries, T2-fluid attenuated inversion recovery (FLAIR) and a blood-sensitive sequences such as gradient-recalled echo (GRE) or susceptibility weighted imaging (SWI).<sup>44</sup>

### **Principles of acute stroke care**

The main objective of acute ischaemic stroke treatment is to salvage ischaemic, but viable, brain tissue by recanalising occluded cerebral arteries and reperfusion the ischaemic penumbra.<sup>45</sup> The penumbra is a region of electrically inexcitable, hypoperfused parenchyma surrounding the irreversibly damaged core<sup>46</sup> that is temporarily supported by leptomeningeal collateral flow. Failure to recruit or maintain collaterals underlies the highly variable individual speed of evolution of the core and mechanisms of collateral failure are currently poorly understood.<sup>47</sup> Rapidly declining benefit from reperfusion therapies (*'time is brain'*)<sup>48</sup> reflects the average pathophysiological status of failure of collateral support over several hours. In some individuals, identified by imaging, collaterals are maintained for longer periods, and later reperfusion is beneficial. *Figure 2* offers a structured approach to acute stroke



reperfusion; it is an overview of 'best practice' and should be used in conjunction with local protocols which will be tailored to available services where necessary.

Patients with severely elevated BP ( $\geq 185$ mmHg systolic or  $\geq 110$ mmHg diastolic) are precluded from thrombolysis due to alteplase licencing restrictions and may require intravenous anti-hypertensive therapy<sup>9</sup> (e.g. intravenous labetalol 5-10mg or glyceryl trinitrate 50mg in 50ml starting at 1.5ml/ hour). However, the BP threshold is based on the original alteplase trial inclusion criteria<sup>49</sup> and there is no evidence that reducing BP in this context is clinically beneficial; indeed, recent data suggest a complex interaction between reperfusion status, BP and patient outcome, with one study suggesting BP-lowering may be inappropriate before reperfusion treatment.<sup>50</sup>

### **Acute reperfusion strategies**

#### *Intravenous thrombolysis*

Tissue-type plasminogen activator (tPA) cleaves plasminogen on the surface of thrombi to form plasmin, a powerful endogenous fibrinolytic enzyme.<sup>51</sup> Intravenous recombinant tPA (rtPA, alteplase) is proven and licenced to improve functional outcome in acute ischaemic stroke up to 4.5 hours after symptom onset.<sup>10,52</sup> The treatment effect is heavily time-dependent: the number needed to treat (NNT) for excellent functional outcome at 1.5 hours is five, compared with nine at 3-4.5 hours.<sup>53</sup> The relative benefit of rtPA is not modified by baseline stroke severity or age.<sup>53,54</sup>

UK guidelines recommend all patients with disabling symptoms should be considered for rtPA treatment within 3 hours of symptom onset and up to 4.5 hours in those under the age of 80. Patients presenting 4.5 to 6 hours should be considered on an individual basis for treatment, recognising that the benefits are smaller than if treated earlier, but that the risks of a worse outcome, including death, are not increased.<sup>55</sup> The UK performs poorly compared to other countries, both in the proportion of patients receiving rtPA (12% for the past 6 years<sup>56</sup>) and mean door-to-needle times (52 minutes last year in England and Wales<sup>57</sup>); considerable improvements in outcome are achievable if these could be bettered.

Informed consent is rarely possible and should not delay treatment. In one registry of nearly 2,000 patients, a median door-to-needle time of only 20 minutes included a consent discussion of less than a minute,<sup>58</sup> however if unavailable, treatment should proceed in the patient's best interests.

Currently there is little evidence to support thrombolysis in patients with non-disabling ischaemic stroke.<sup>59</sup> The relative and absolute contraindications to rtPA are shown in *Table 2*. Symptomatic ICH (sICH) is the most feared adverse effect of rtPA but haemorrhage

associated with significant neurological deterioration occurs in only approximately 1.9% of treated patients.<sup>60,61</sup> Radiological haemorrhagic transformation occurs due to reperfusion and is more common in larger infarcts (therefore more severe baseline deficits). Neurological deterioration after rtPA infusion is common but usually reflects the initial ischaemic injury; in one recent case series, only one of 511 patients deteriorated during the rtPA infusion due to ICH, the majority of ICH-related deterioration occurred after the complete rtPA infusion, and deterioration due to initial ischaemia was four times more likely than ICH.<sup>62</sup> Urgent repeat neuroimaging is needed to clarify the cause and rtPA infusion is commonly suspended pending imaging.

Orolingual angioedema is a recognised complication of rtPA; whilst the majority of cases are mild and self-limiting, severe attacks requiring airway management can occur in up to 1% of treated patients, with those on angiotensin-converting enzyme inhibitors or with insular ischaemia at increased risk.<sup>63</sup> Local protocols for the assessment and urgent management of angioedema should be developed with the anaesthetic department. Although management in this setting is not evidence based, treatment should be consistent with that of other drug reactions (Figure 3).

### *Endovascular thrombectomy*

Despite the overall benefit of rtPA, the subgroup of patients with large proximal intracranial vessel occlusion (LVO; carotid, proximal middle cerebral arteries) have low rates of recanalisation with thrombolysis and only a 25% chance of a good outcome.<sup>64,65</sup>

Endovascular thrombectomy (EVT) in addition to best medical therapy has been proven in nine randomised trials as superior to best medical therapy alone (including intravenous rtPA in the majority of patients) for patients with anterior circulation LVO.<sup>66–74</sup> The NNT to achieve a reduction of one or more points on modified Rankin Scale (mRS) is 2.6.<sup>75</sup> A detailed guide has recently been published in *Practical Neurology*.<sup>76</sup>

Unfortunately, the UK has been slow to provide this service; current EVT rates are 5.5 per 1000 ischaemic strokes in the UK versus 50 in the US and Western Europe.<sup>56</sup> Parts of the UK, notably Scotland, have no access to thrombectomy at all. In England and Wales, the NHS Long Term Plan aims for a 10-fold increase by 2022, in part by expanding EVT training to specialities other than interventional neuroradiology.<sup>4</sup>

NICE guidelines recommend EVT for patients with disabling acute ischaemic stroke (arbitrarily defined as NIHSS $\geq$ 6) due to imaging-proven anterior circulation LVO up to six hours and posterior circulation (basilar or posterior cerebral artery) LVO up to 24 hours after symptom onset.<sup>10</sup> Patients with lower NIHSS but functionally disabling symptoms may also be considered due to the high risk of LVO associated deterioration.<sup>77</sup>

As with rtPA, the benefit of EVT is highly time dependent.<sup>78</sup> However, several clinical trials demonstrated favourable outcome of EVT versus medical management in anterior circulation LVO beyond six hours, albeit based on small numbers of patients.<sup>67,70,79</sup> Two trials have extended the therapeutic window even further: up to 16 hours in DEFUSE 3<sup>80</sup> and 24 hours in DAWN<sup>81</sup> with CT perfusion or DWI-perfusion imaging with clinical mismatch. These trials demonstrated that imaging can select LVO patients likely to benefit from EVT due to good collateral supply.

The optimal mode of anaesthesia during EVT has yet to be determined; retrospective data has suggested general anaesthesia to be harmful (although potentially biased by patient selection),<sup>82</sup> whereas single-centre randomised trials have shown neutral or beneficial effects.<sup>83</sup> Multicentre randomised trials are ongoing.<sup>76</sup>

The complication rates of EVT are in keeping with other emergency procedures and serious adverse events are rare.<sup>84</sup> Although adverse events occur in approximately 15% of patients (including vasospasm, arterial perforation or dissection, device misplacement, sICH or embolisation to new or target vessel territory), clinical outcome is not affected overall; the NNT of 2.6 includes these complications.<sup>85</sup>

#### *Acute stroke unit and early complications*

Guidelines recommend all acute ischaemic stroke patients are admitted directly to an Acute Stroke Unit (ASU).<sup>9</sup> Stroke unit care has an NNT of 17 to avoid death or disability, a benefit which is sustained over time without lengthening hospital stays.<sup>86,87</sup> Key features of the ASU include stroke-specific multidisciplinary care (physiotherapy, speech and language therapy, occupational therapy) and high nursing ratios.<sup>88,89</sup> However, for the past five years only 58% of patients in England and Wales were admitted to an ASU within four hours.<sup>57</sup>

Prevention of secondary brain insults by maintaining physiological homeostasis (*Table 2*) and monitoring neurological status is a key function of the ASU.<sup>90</sup> The patient should also receive bedside cardiac telemetry if atrial fibrillation has not been confirmed.

Neurological deterioration should prompt urgent repeat neuroimaging; early neurological complications include recurrent ischaemia, cerebral oedema or haemorrhagic transformation. Repeat brain imaging around 24 hours following rtPA administration is widely undertaken to inform on ICH incidence as a quality of care metric, and visualisation of an infarct may provide prognostic and mechanistically relevant information, but the role for routine repeat imaging is debatable. Once haemorrhagic complications have been excluded at 24 hours antiplatelet therapy should commence, most often 300mg aspirin daily for two weeks followed by lifelong clopidogrel monotherapy.

Patients with acute occlusion of the proximal MCA or internal carotid artery (ICA) and large volume hemispheric infarcts are particularly vulnerable to 'malignant' cerebral oedema, which has a mortality rate of up to 78%.<sup>91</sup> Decompressive hemicraniectomy (DHC) increases the chance of survival (NNT of 2) but patients are often left with significant disability (mRS 4-5 at 1 year in 43% with DHC vs 17% with medical management),<sup>92</sup> however the great majority rate their quality of life as satisfactory despite disability.<sup>93</sup> Updated NICE guidance<sup>10</sup> has removed the upper age limit for consideration of DHC, in line with trial evidence; the current eligibility criteria are:

- Surgery can be performed 48 hours from stroke onset
- Clinical deficits suggest of MCA infarction with NIHSS>15
- Decreased level of consciousness ( $\geq 1$  on level of consciousness on NIHSS)
- Infarction of  $\geq 50\%$  of MCA territory as seen on CT or infarct volume  $>145\text{cm}^3$  on DWI

The high incidence of dysphagia after stroke is a risk factor for aspiration pneumonia and is associated with increased mortality and disability.<sup>94</sup> Guidelines recommend that patients receive a bedside swallowing assessment and appropriate adaptation of oral intake to prevent aspiration.<sup>10</sup> Although there are no randomised studies to determine whether screening methods improve outcomes,<sup>95</sup> observational data suggest that delayed assessment is associated with a higher risk of aspiration pneumonia.<sup>96</sup> Prophylactic antibiotics have not proven effective.<sup>97</sup>

Non-ambulatory ischaemic stroke patients are at high risk of deep vein thrombosis (DVT).<sup>98</sup> Prophylaxis with low molecular weight heparin is not recommended due to the risk of haemorrhagic transformation<sup>9</sup>, although some data have shown no significant additional risk.<sup>99</sup> Compared to compression stockings, intermittent pneumatic compression devices are effective at reducing the risk of DVT and are recommended for all non-ambulatory stroke patients.<sup>9,100</sup>

### **Future directions**

There is a wealth of active clinical research in stroke medicine, driven by the significant public health implications of this common and socioeconomically impactful disease. Of particular priority in the UK is improving systems to reduce onset-to-needle times, increase access to EVT and ASU admission rates. Audits, including the *Sentinel Stroke National Audit Programme* (SSNAP), measure the processes and structure of stroke care and use these data to drive improvements.

Mobile stroke units with in-built CT scanners and telemedicine links with stroke centres are associated with earlier thrombolytic delivery and improved clinical outcome in urban settings, but are resource intensive and optimal deployment is dependent on accurate pre-hospital triage.<sup>101</sup>

Alternatives to alteplase that are more fibrin-specific may be safer, more effective, and may increase the therapeutic window. However, desmoteplase did not improve functional outcome compared to placebo in acute ischaemic patients 3-9 hours after symptom onset<sup>102</sup> and although tenecteplase has not proven superior to alteplase in minor ischaemic stroke patients<sup>103</sup> (a trial in patients with non-disabling symptoms due to LVO is ongoing<sup>40</sup>) it doubled recanalisation rates in pre-endovascular treatment of LVO strokes with improved functional outcome.<sup>104</sup> In addition, the single bolus administration of tenecteplase may be advantageous for drip-and-ship thrombectomy service pathways.

Ongoing trials are investigating the efficacy of EVT in patient subgroups, including basilar artery occlusion (BASICS<sup>105</sup>), low NIHSS (MOSTE<sup>106</sup> and ENDOLOW<sup>107</sup>), or low ASPECTS score (TESLA,<sup>108</sup> TENSION<sup>109</sup> and IN EXTREMIS<sup>106</sup>). The optimal pre-hospital service pathway is another unanswered question, and mothership and drip-and-ship models are also being compared in a multicentre trial.<sup>110</sup>

Multiple pre-clinical and clinical studies to prevent secondary neuronal injury following ischaemic stroke have been unsuccessful and to date there are no evidence-based neuroprotective agents.<sup>111</sup> Although the neuroprotectant nerinetide did not improve outcomes in endovascular-treated patients compared to placebo in one recent randomised trial, secondary subgroup analyses suggest further investigation may be warranted in patients not treated with alteplase.<sup>112</sup> Translational studies of neuroprotective therapies may be aided by novel tissue banking of thrombi extracted by EVT.<sup>113</sup> The CHARM trial aims to assess whether Glibenclamide (BIB093) improves functional outcome in patients with malignant brain oedema.<sup>114</sup>

## Conclusion

Stroke medicine is a varied and rapidly developing field which provides the opportunity to offer life-changing treatments to patients affected by the leading cause of neurological disability. Stroke care will have increasing relevance for neurologists of the future and as a speciality we have a lot to offer, in particular with diagnostic expertise. Equally, we may need to develop our skills further, for example the management of acutely unwell patients with

general medical problems on the ASU or by learning how to perform mechanical thrombectomy.

**Competing interests**

The authors report no personal or financial conflicts of interests.

**Acknowledgements**

There are no acknowledgements relevant to this manuscript.

**Contributorship**

RH drafted the manuscript. Other authors revised the manuscript.

**Funding info**

There is no specific funding associated with this manuscript.

**Ethical approval information**

Ethical approval was not required for this manuscript.

**Data sharing statement**

Not applicable.

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**Table 1:** Large vessel stroke syndromes (assumes left hemispheric dominance). Adapted from Southerland *et al.*<sup>122</sup>

<b>Vascular territory</b>	<b>Signs and symptoms</b>
Internal carotid artery	Combined anterior cerebral artery/middle cerebral artery syndromes; ipsilateral monocular visual loss secondary to transient central retinal artery occlusion (amaurosis fugax); branch retinal artery occlusions may present as ipsilesional altitudinal field cuts.
Anterior cerebral artery	Contralateral leg numbness and weakness, possibly ipsilateral ('sympathetic') or contralateral ideomotor apraxia, (L) transcortical motor aphasia, (R) motor neglect. Occasionally urinary incontinence (medial micturition centre), ipsilateral eye deviation and paratonic rigidity.
Middle cerebral artery	Superior division (lateral frontal and superior parietal lobes): contralateral face/ arm (more than leg) numbness and weakness, contralateral homonymous hemianopia (lower fields), cortical hand syndrome*, ipsilateral gaze preference, [dom] expressive aphasia, [non-dom] contralateral hemispatial neglect, agrapheaesthesia, astereognosis. Inferior division (lateral temporal and inferior parietal lobes): contralateral homonymous hemianopia (upper fields), [dom] receptive aphasia, [non-dom] constructional apraxia.
Posterior cerebral artery <sup>†</sup>	Complete or partial contralateral homonymous hemianopia, if midbrain involvement ipsilateral third nerve palsy with mydriasis and contralateral hemiparesis (Weber syndrome), (L with splenium of corpus callosum) alexia without agraphia.
Superior cerebellar artery	Ipsilateral limb and gait ataxia.
Anterior inferior cerebellar artery	Vertigo and ipsilateral deafness, possibly also ipsilateral facial weakness and ataxia.
Vertebral/ posterior inferior cerebellar artery	Ipsilateral limb and gait ataxia; if lateral medullary involvement, may have ipsilateral fifth cranial nerve, cerebellar, nucleus ambiguous (hoarseness and dysphagia), vestibular nucleus dysfunction, Horner's syndrome and contralateral hemisensory loss to pain and temperature (Wallenberg syndrome).
Basilar artery	Pontine localisation with impaired lateral gaze, horizontal diplopia and disconjugate gaze, non-localised hemiparesis, dysarthria; "locked-in syndrome" with bilateral pontine infarction (intact vertical eye movements, anarthria, quadriplegia).

R= right hemisphere, L= left hemisphere.

\*Targeted infarct of the precentral motor hand cortex ('hand knob') often associated with ipsilateral internal carotid stenosis, causing deficit involving only the contralateral hand, several fingers, or just the thumb.<sup>123</sup> <sup>†</sup> Note the potential for paradoxical embolisation from the anterior to posterior territory in patients with fetal-origin posterior circulation arteries (posterior cerebral arteries arising from the distal internal carotid artery - a normal anatomical variant) and for a detailed review of the vascular supply of the thalamus, see Powell *et al.*<sup>124</sup>



**Table 2:** Targets for maintaining homeostasis in acute ischaemic stroke patients. Adapted from National Clinical Guideline for Stroke 2016.<sup>9</sup>

Parameter	Target/ intervention
Oxygen saturation	Oxygen supplementation if saturation <95%
Hydration	Assessed within 4 hours using multiple tools
Swallowing	Screen for dysphagia with validated tool within 4 hours and before any oral intake (including medication)
Serum glucose	5-15 mmol/L
Blood pressure	No target. Indication for treatment: <ul style="list-style-type: none"> <li>- <math>\geq 185</math> or <math>\geq 110</math> mmHg</li> <li>- Hypertensive encephalopathy, nephropathy, cardiac failure or myocardial infarction</li> <li>- Aortic dissection</li> <li>- Pre-eclampsia/ eclampsia</li> </ul>

**Table 3:** American Heart Association/ American Stroke Association absolute and relative contraindications to treatment of acute ischaemic stroke with alteplase. Abridged from Demaerschalk *et al.*<sup>125</sup>

<b>Absolute contraindications</b>		<b>Comments regarding alteplase (rtPA) use</b>
Systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg		Treatment recommended if blood pressure can be lowered
International normalised ratio (INR) >1.7		Must be tested if patient taking Warfarin, rapid point of care testing can be used in the hyperacute setting.
Direct oral anticoagulant (DOAC) use within 48 hours		Safety of thrombolysis in patients on DOACs is not well studied. Direct factor Xa assays may become a fast and reliable method of measuring direct factor Xa inhibitor activity (Apixaban and Rivaroxaban) and dilute thrombin time is sensitive to the presence of Dabigatran activity but more research is required. <sup>†</sup>
Platelets <100,000/mm <sup>3</sup>		Serum platelet level not required before rtPA unless low platelet count is suspected.
Active internal bleeding		Low bleeding risk in those with past (>21 days) gastrointestinal bleeding.
Intracranial or intraspinal surgery or severe head trauma within 3 months		No high quality evidence but the location of potential surgical site bleeding may limit benefits of rtPA compared to general surgical patients.
Intracerebral vascular malformations		Including cavernous angioma, capillary telangiectasia, developmental venous anomalies and arteriovenous malformations. Insufficient data and large variation in haemorrhage risk.
Intracranial malignancy		rtPA should be safe with extra-axial but not recommended in those with intra-axial malignancy.
Previous intracranial haemorrhage (ICH)		'Recent' history of previous ICH in recent FDA label. Limited data but increased risk of sICH seems related to volume of encephalomalacia from ICH, same vascular territory as ischaemic event and how recent. CMBs have not been shown to increase risk of sICH.
Ischaemic stroke within 3 months		Limited data to suggest increased risk of adverse events. Contraindication removed from updated FDA licence.
Arterial puncture at non-compressible site within 7 days		Including subclavian or jugular catheterisation.
Infective endocarditis		Cerebral infarcts caused by septic emboli are prone to haemorrhagic transformation due to septic arteritis.
<b>Relative contraindications</b>		
Rapidly improving symptoms		rtPA recommended if symptom improvement but remains disabled.
Pregnancy and early postpartum (<14 days)		Insufficient data, case by case risk decision with obstetric team.
Unruptured intracranial aneurysm (UIA)		Small (<10mm) unsecured UIA should not preclude rtPA, insufficient data on larger UIA.
Seizure at onset		Concerns of diagnostic uncertainty (post-ictal neurological deficits).
Major extracranial trauma within 14 days		Limited data. One small meta-analysis of rtPA use in cervical artery dissection (including some trauma-related) reported no safety concerns.

Major surgery within 14 days or gastrointestinal or genitourinary surgery within 21 days	Including CABG, organ biopsy or child birth and relates to increased risk of surgical site haemorrhage. Limited data so not an absolute contraindication, but case by case risk decision.
Acute myocardial infarction (MI) within 3 months	rtPA recommended if concurrent MI and ischaemic stroke. If history of MI within the last 3 months, rtPA is reasonable if non-STEMI or right/ inferior myocardial STEMI. Lower class of evidence for left anterior myocardial STEMI.

*rtPA= recombinant tissue-type plasminogen activator (alteplase), sICH= symptomatic intracerebral haemorrhage, CABG= coronary artery bypass surgery, STEMI- ST-elevation myocardial infarction, NSTEMI= non-ST-elevation myocardial infarction.*

<sup>¶</sup> The European Heart Rhythm Association recommends considering thrombolysis if DOAC plasma level is below the lower limit of detection (or <30ng/ml for Xa inhibitors if >4 hours after intake) or last dose within 24-48 hours and normal renal function.<sup>126</sup> One meta-analysis has indicated no increased risk of sICH with prior DOAC use patients treated with IVT and reports successful thrombolysis after Dabigatran reversal with Idarucizumab.<sup>127</sup> Andexanet alfa is FDA-approved for Xa inhibitor reversal but is not currently licensed in the UK.

**Figure Legends**

**Figure 1:** Eligibility, investigations, diagnosis and treatment in a rapid access TIA clinic.

**Figure 2:** Process of acute ischaemic stroke reperfusion therapy: an overview of 'best practice'

**Figure 3:** Suggested treatment algorithm for rtPA associated angioedema