Abstract

Intravenous Thrombolysis (IVT) significantly increases the chance of functional independence post-stroke, and an improved understanding of delivery has ensured better safety and clinical outcomes. Despite this, there remain several aspects of IVT delivery that are yet to be clarified including: the role of new thrombolytic agents; treatment strategies for stroke with unknown onset time, including wake-up stroke; and the role of an intensive peri-thrombolysis BP target. Tenecteplase is an emerging IVT agent that has preferential characteristics yet to be fully examined in larger studies of AIS patients or sub-groups including ‘wake-up’ stroke. We await the results of on-going trials to ensure continuing optimisation of IVT delivery.
Key Points

- Despite significant advancement in the delivery of intravenous thrombolysis (IVT) for acute ischaemic stroke (AIS), several unanswered questions remain.
- There is no upper age limit for delivery of IVT in AIS but consideration for individualised patient factors is crucial when co-morbidity exists.
- Despite continuing deliberation as to blood pressure (BP) lowering in AIS, randomised controlled trials are soon to report, specifically in an IVT population.
- MRI-guided delivery of IVT in ‘wake-up’ AIS marks a significant step forward, though concern regarding resource allocation may hinder wider usage.
- Though alteplase remains the mainstay of IVT therapy worldwide for AIS, tenecteplase is an emerging IVT agent with advantageous pharmacokinetic properties, and resulted in a higher incidence of reperfusion in a small trial of IVT before thrombectomy.
- Further trials are underway to compare efficacy of tenecteplase to alteplase in larger studies of AIS patients and in specific sub-groups, including ‘wake-up’ AIS populations.

Key Words: Acute Stroke, Guidelines, Thrombolysis, Blood Pressure, Novel Therapies
Background

The last decade has seen a significant refinement in the delivery of cerebral reperfusion therapy. Despite the advent of mechanical thrombectomy (Goyal, Menon et al. 2016, Royal College of Physicians Intercollegiate Stroke Working Party 2016), intravenous thrombolysis (IVT) is likely to remain the mainstay of therapeutic reperfusion for the majority of acute ischaemic stroke (AIS) patients worldwide. For IVT, the number needed to treat (NNT) for best functional outcome is 5 for treatment within 90 minutes of AIS onset, underlining the ‘time is brain’ hypothesis (Emberson, Lees et al. 2014). This progress is largely driven by advancement in our understanding of approaches to managing large vessel occlusion through better radiological imaging, randomised controlled trial data (RCTs), and improvement in pre-hospital and early hospital pathways with a focus on onset- and door-to-needle times. The importance of consideration of service delivery on IVT rates should not be downplayed, particularly as it can maximise IVT rates to 20% based on current guidelines (Morris, Rosamond et al. 2000). Nonetheless, several clinically important research questions remain unanswered, including minimising the risk of symptomatic intracerebral haemorrhage (sICH) through improved patient selection, managing ‘wake-up’ stroke, peri-thrombolysis blood pressure management, and efficacy and safety of emerging thrombolytic agents (for example, tenecteplase). This brief review will expand on current guidelines and highlight emerging evidence supporting these areas of current uncertainty.
National Clinical Guidelines

The most recent United Kingdom Stroke National Clinical Guidelines (2016) provide an important summary of the evidence associated with current stroke management recommendations (Royal College of Physicians Intercollegiate Stroke Working Party 2016). These guidelines emphasise key aspects of thrombolysis delivery including licensing of alteplase, time to alteplase delivery, patient selection, dosage of alteplase, as well as considerations for sICH risk (Royal College of Physicians Intercollegiate Stroke Working Party 2016). Key IVT developments in this guideline based on updated Cochrane meta-analyses (Wardlaw, Murray et al. 2012) and new RCT evidence (Anderson, Robinson et al. 2016) were the consideration of alteplase delivery for over 80 year olds and consideration for usage of low dose alteplase, respectively. First, the Cochrane review and meta-analysis showed that older patients (>80 years) benefit as much as those <80 years particularly if alteplase is delivered within the first 3 hours, thus highlighting the redundancy of an upper age limit (Wardlaw, Murray et al. 2012, Emberson, Lees et al. 2014). Secondly, the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) randomised controlled trial comparing low- (0.6mg/kg body weight) versus standard-dose (0.9mg/kg body weight; 10% as bolus injection over two minutes, the remainder administered as an infusion over an hour) alteplase demonstrated significantly lower sICH rates and 7-day mortality with low-dose therapy, but overall did not demonstrate non-inferiority with respect to a 90-day dichotomised functional outcome (Anderson, Robinson et al. 2016). Nonetheless, standard-dose alteplase remains the mainstay of IVT therapy, delivered as soon as possible within a 4.5-hour time window for patients under 80 years old, and within a 3-hour time
window for over 80 year olds. For those over 80 years old, alteplase should be considered in the 3- to 4.5-hour time window on an individual basis. There may be circumstances where low-dose could be considered by the treating physician and/or patient though further research is required to define this group, potentially on the basis of co-morbidities and extent of pre-existing radiologically evident burden of cerebrovascular disease.

**Tenecteplase**

Tenecteplase (TNK) is a modified tissue plasminogen activator with preferential pharmacokinetics over its comparator alteplase. An individual patient data meta-analysis of 291 AIS (phase II trial) participants recommended further studies of 0.25mg/kg TNK, as there was no significant difference between TNK and alteplase for efficacy or safety (Huang, Maclsaac et al. 2016). The Norwegian NOR-TEST trial failed to show superiority (and was not pre-specified as ‘non-inferiority’) of 0.4mg/kg TNK over alteplase in 1,100 AIS patients, in part related to low disability outcome from having a high number of patients with transient ischaemic attack (TIA), minor AIS, and ‘stroke mimics’ (Logallo, Novotny et al. 2017). However, the recently completed Australian EXTEND-IA-TNK trial showed superiority of TNK 0.25mg/kg over alteplase for a radiological (early recanalisation) and not clinical outcome, in 202 highly selected thrombectomy-eligible AIS patients (Campbell, Mitchell et al. 2018). Accordingly, several studies are ongoing to assess tenecteplase versus alteplase in thrombolysis-eligible AIS patients (Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis [ATTEST-2] ClinicalTrials.gov Identifier NCT02814409, as well as in highly selected patients groups, including minor
ischaemic stroke with large vessel occlusion (A Randomized Controlled Trial of TNK-TPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion [TEMPO-2] ClinicalTrials.gov Identifier NCT02398656), evidence of ischaemic penumbra on perfusion imaging (Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation [TASTE] ANZCTR Identifier ACTRN12613000243718), and in wake-up stroke (Tenecteplase in Wake-Up Ischaemic Stroke Trial [TWIST] ClinicalTrials.gov Identifier NCT03181360).

Wake-Up Stroke

In the absence of a defined onset time for AIS, IVT is contraindicated. However, radiological advancement has provided a culture shift away from duration of symptoms predicting reversibility of ischaemic burden to image guided assessment of volume of ischaemic and infarcted cerebral matter. If a ‘mis-match’ (between MRI diffusion weighted imaging and FLAIR) exists, this suggests a salvageable penumbra perhaps benefiting from IVT therapy. Such a hypothesis was tested in the Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke (WAKE-UP), with AIS patients treated with alteplase compared to placebo had a significantly better 90-day functional outcome (Thomalla, Simonsen et al. 2018). A potential rate-limiting factor associated with implementation of this study into clinical practice is the availability of ‘front-door’ MRI. The on-going CT-based wake-up stroke trial, TWIST, may help answer this.

Blood Pressure

There is on-going controversy with respect to the management of many physiological perturbations in acute stroke, including blood pressure (Appiah,
Minhas et al. 2018). In particular, very little data exist to support intensive BP lowering in the IVT eligible population, though systolic hypertension appears to be associated with an increased sICH risk (Ahmed, Wahlgren et al. 2009). The ENCHANTED study also included a BP arm to compare intensive (130-140mmHg systolic target) versus current guideline (180mmHg systolic target) in IVT patients, and is anticipated to present its results in 2019. Furthermore, collaborative approaches using individual patient data meta-analyses are underway to better understand the position of equipoise that exists when considering lowering BP in AIS (Sandset, Sanossian et al. 2018).

**Conclusion**

IVT significantly increases the chance of functional independence post-stroke, and an improved understanding of delivery has ensured better safety and clinical outcomes. Despite this, there remain several aspects of IVT delivery that are yet to be clarified including: the role of new thrombolytic agents; treatment strategies for stroke with unknown onset time, including wake-up stroke; and the role of an intensive peri-thrombolysis BP target. We await the results of on-going trials, including those described previously, to provide further refinement to ensure optimal IVT delivery.
References


