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CLINICAL COMMENTARIES
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Reperfusion in the brain: is time important? The DAWN and DEFUSE-3 trials

Thompson Robinson*

Department of Cardiovascular Sciences, University of Leicester, BHF Cardiovascular Research Centre, The Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK

Professor Tom Robinson is Head of the Department of Cardiovascular Sciences at the University of Leicester, National Specialty Lead for the National Institute for Health Research Clinical Research Network, and President of the British Association of Stroke Physicians. Professor Robinson works as a Stroke Physician, and his research focus is on clinical trials in acute stroke, particularly blood pressure and thrombolysis management, and studies of cardiovascular and cerebrovascular regulatory mechanisms.

Commentary on 'Thrombectomy 6 to 24 h after stroke with a mismatch between deficit and infarct' by Nogueira *et al.*, *N Engl J Med*, 2017.[1]

Reperfusion therapy using intravenous thrombolysis[2] and mechanical thrombectomy[2,3] are the only approved treatments for acute ischaemic stroke, but must be administered in a narrow therapeutic window of up to 4.5 and 6 h, respectively.[4,5] A further meta-analysis by the HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials) collaboration has suggested that mechanical thrombectomy may be beneficial up to 7.3 h after stroke onset.[6] However, the results of the DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo)[1] and the DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischaemic Stroke)[7] trials may extend this window up to 24 h in carefully selected patients.

The DAWN trial, the first study to compare endovascular therapy with standard medical care for patients with acute ischaemic stroke who were last known well 6 to 24 h earlier, has now been reported.[1] In this multi-centre, prospective, open-label trial with blinded outcome assessment, 206 patients with occlusion of the intracranial internal carotid, proximal middle cerebral artery, or both on computed tomographic (CT) or magnetic resonance (MR) angiography and mismatch between the severity of clinical deficit and infarct volume were randomly assigned to thrombectomy plus standard medical care vs. standard medical care alone. Mismatch was defined by: (i) aged 80 years and older with National Institutes of Health Stroke Scale (NIHSS) score of 10 or more and infarct volume of less than 21 mL assessed by diffusion-weighted MR or perfusion CT using automated software (RAPID, iSchaemiaView); (ii) aged younger than 80 years with NIHSS score of 10 or more and infarct volume of less than 31 mL; or (iii) aged younger than 80 years with NIHSS score of 20 or more and infarct volume of 31 to 50 mL. Compared to standard medical care alone, thrombectomy was associated with significant benefit on the 90-day co-primary outcome with a utility-weighted modified Rankin score (mRS) of 5.5 (vs. 3.4; range of scores 0 [death] to 10 [no symptoms or disability]) and rate of functional independence, defined by mRS of 0 to 2, of 49% (vs. 13%).

The recently published results of the DEFUSE 3 trial have further confirmed the use of advanced neuroimaging techniques to define an acute ischaemic stroke population that may benefit from thrombectomy in an extended time window.[7] In this multi-centre, open-label trial with blinded outcome assessment, 182 patients, between 6 and 16 h after the time last known well, had been randomized to thrombectomy plus medical therapy vs. medical therapy alone, prior to early trial termination for efficacy. Patients were eligible if they had an initial infarct volume of less than 70 mL, a ratio of volume of ischaemic tissue to initial infarct volume of 1.8 or more, and an absolute volume of potentially reversible ischaemia of 15 mL or more, assessed from CT perfusion or MR diffusion, and perfusion scans using automated software (RAPID, iSchaemiaView). Compared to medical therapy alone, thrombectomy was associated

* Corresponding author. Tel: +44116 204 4752, E-mail: tgr2@leicester.ac.uk

with a favourable mRS shift at 90 days (odds ratio 2.77, 95% confidence interval 1.63 to 4.70, $P < 0.001$). Benefit was independently seen for both patient groups that did (and did not) meet the DAWN eligibility criteria.

Therefore, the DAWN and DEFUSE 3 trials have led to a Level I-A recommendation in the most recent American Heart Association and American Stroke Association acute ischaemic stroke guidelines that selected patients within 6 to 24 h of last known well benefit from thrombectomy, when the imaging and other eligibility criteria from DAWN and DEFUSE 3 are strictly applied.[4] These guidelines raise many challenges for the stroke community, in particular in relation to the organization of services to ensure rapid transfer of eligible patients to centres that can provide thrombectomy, timely assessment of suspected acute ischaemic stroke patients with access to multi-modal advanced imaging and its interpretation, and a sufficient and trained multi-disciplinary workforce to deliver specialist pre-, peri-, and post-thrombectomy care.

In addition, the results of these trials provided exciting basic science, translational and clinical research opportunities. The use of neuroprotective agents has been a notable failure of translation from basic science research into clinical practice, but mechanical thrombectomy, and in particular the ability of advanced neuroimaging to identify a favourable population for intervention, highlights the opportunity to re-examine neuroprotective agents as adjunct therapies to recanalization. However, this requires collaboration with the basic and translational science community, in a number of domains.[8] For example: (i) use of appropriate pre-clinical models, including duration of transient ischaemia that is appropriate to the time course of interventional therapy (intraluminal filament models may more accurately reflect the patient suitable for mechanical thrombectomy, and neuroprotection should be reassessed in this context); (ii) use of models that more typically reflect the older co-morbid human population (acknowledging the importance of phenotype, both preclinical and clinical in the response to MT); (iii) use of a multi-omics approach to target identification, target validation, lead discovery and optimization, and pharmacology; (iv) adoption of phase III multi-centre preclinical trial methodology; and (v) robust reporting of positive, neutral and negative studies (including on-going individual animal data meta-analysis).[8] Importantly, the use of imaging paradigms for selection and endpoints in preclinical studies, including assessment of the collateral circulation, are particularly important, as the DAWN and DEFUSE 3 trials have highlighted the need to identify a population of 'slow progressors'; those fortunate patients with favourable collaterals and slow infarct growth.[9] Furthermore, though thrombectomy-associated rates of symptomatic intracranial haemorrhage were low in DAWN (6%)[1] and DEFUSE 3 (7%),[7] and comparable with the medical therapy groups (3% and 4%, respectively), research is still required to predict and minimize this feared complication of therapeutic and mechanical reperfusion, including the use of pre-clinical models that mimic this complication of reperfusion therapy.

In addition, there is an opportunity to research strategies that restore microvascular, as well as macrovascular, cerebral blood flow to prevent exacerbation of ischaemic damage already caused, but also to explore novel neuroprotective strategies that modulate factors that may exacerbate this damage, through drugs that target excitotoxicity, oxidative stress, and inflammatory processes, and that promote neurorepair.[8] For example, NA-1 is a peptide that disrupts interactions between NMDA receptor subunits, post-synaptic density-95, and neuronal nitric oxide, and has showed evidence of protective properties.[10] The potential benefits of pre-hospital administration is currently being explored in the FRONTIER (Field Randomization of NA-1 Therapy in Early Responders) trial [NCT02315443], including eligibility for endovascular recanalization in a 24-h time window as a secondary objective.

In conclusion, the DAWN and DEFUSE 3 trials provide an exciting opportunity to extend reperfusion therapies to an appropriately selected ischaemic population up to 24 and 16 h, respectively. The challenge for the clinical stroke community is to deliver this benefit; the opportunity for the preclinical and translational stroke community is to develop new strategies for stroke treatment, as well as to re-visit the previous treatment paradigms that translated without success.[11]

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