Perfusion imaging in acute ischaemic stroke – the beginning of the end?

Authors: Permesh Singh Dhillon,[A] Phil White,[B] Mayank Goyal,[C] Wim H van Zwam[D] and Robert Lenthall[A]

ABSTRACT

Endovascular thrombectomy (EVT) for large vessel occlusion in acute ischaemic stroke is the standard of care when initiated within 6 hours of stroke onset, and is performed between 6–24 hours using advanced neuroimaging (CT perfusion or MR imaging) for patients who meet the strict imaging selection criteria. However, adherence to the restrictive imaging criteria recommended by current guidelines is impeded in many parts of the world, including the UK, by resource constraints and limited access to advanced neuroimaging in the emergency setting. Furthermore, recent randomised and non-randomised studies have demonstrated that patients selected without advanced neuroimaging (with non-contrast CT and CT angiography only) using less restrictive imaging criteria for EVT eligibility beyond 6 hours from onset still benefited from EVT treatment, thereby increasing the proportion of patients eligible for EVT and widening the potential treatment impact at a population level. Hence, current guidelines should be updated expeditiously to reflect the level I evidence in support of more liberal imaging selection criteria for patients presenting with acute ischaemic stroke due to a large vessel occlusion.

KEYWORDS: stroke, thrombectomy, CT, imaging, perfusion

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Following publication of the landmark randomised controlled trials (RCTs) in 2015, endovascular thrombectomy (EVT) for large vessel occlusion in acute ischaemic stroke (AIS) became the standard of care when initiated within 6–12 hours of stroke onset.[1,2] In 2018, the DEFUSE-3 and DAWN 'late-window' RCTs demonstrated benefit of EVT for patients with a suitable infarct core/penumbra ratio or clinical deficit mismatch demonstrated by advanced neuroimaging (CT perfusion or MR imaging), following presentation between 6–16 or 6–24 hours, respectively, from the onset of stroke or last known well.[3,4] The findings indicated that salvageable tissue in patients (deemed 'slow progressors') with a small infarct core and tenacious collateral circulation can persist well beyond 6 hours from stroke onset.

Interestingly, the treatment effect of EVT in the late-window DAWN and DEFUSE-3 trials appeared greater than that of the early-window RCTs. This 'late-window paradox' can be explained by the strict imaging modality selection criteria utilised in the late-window RCTs, where CT perfusion or MR imaging was used to super-select patients with a small infarct core and exclude those with a large infarct volume, giving rise to a cohort of patients who were more likely to achieve functional independence (modified Rankin scale 0–2) at 90 days.[5]

Similarly, greater treatment benefit was observed when perfusion-based imaging was utilised for selection of patients with limited core infarct volumes compared with non-perfusion-based neuroimaging between the early-window RCTs that employed different imaging selection modalities and eligibility criteria.[6] However, this observation should be interpreted with caution when considering the optimal imaging selection paradigm at a population level, due to the denominator fallacy.[7] For example, the yield of improved functional outcomes by super-selecting eligible patients with more favourable target-mismatch profiles on imaging may be at the expense of excluding patients with a broader range of tissue characteristics who could still potentially benefit from the EVT treatment effect.

Following the publication of the DAWN and DEFUSE-3 trials, the current UK National Institute for Health and Care Excellence (NICE), ESMINT and AHA/ASA guidelines, as well as the recently published Getting It Right First Time (GIRFT) stroke report, all recommend the use of CT perfusion or MR imaging together with the strict criteria matching the RCTs' eligibility for patient selection for EVT beyond 6 hours from stroke onset.[8–11] However, adherence to such recommendations is impeded in many parts of the world by resource constraints and limited access to urgent advanced imaging. Routine clinical practice in the UK differs from the clinical trial setting and other developed nations delivering EVT, as many institutions utilise non-contrast CT and CT angiography (NCCT/CTA) only (ie without CT perfusion or MR imaging) to visually estimate the core infarct size (ASPECTS) and collateral supply in both the early and late time windows.

At present, the majority of primary stroke centres (PSCs) in the UK lack adequate facilities to implement round-the-clock CT perfusion or MR imaging for patients who present in the late

Authors: [A]interventional neuroradiologist, Nottingham University Hospitals NHS Trust, Nottingham, UK; [B]interventional neuroradiologist, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; [C]interventional neuroradiologist, University of Calgary, Calgary, Canada; [D]interventional neuroradiologist, Maastricht University Medical Center, Maastricht, the Netherlands

window. Therefore, repeat neuroimaging with CT perfusion may be performed upon arrival at some EVT-capable comprehensive stroke centres (CSCs) following inter-hospital transfer to assess the patient's eligibility for EVT. This has cost implications, increases exposure to radiation for the patient and increases the time delay in initiating *a priori* time-critical EVT treatment, for which every hour's delay reduces the probability of achieving functional independence by 5%.[12] Furthermore, the cohort of patients who do not meet the strict imaging criteria demonstrated on CT perfusion at the CSC may be denied EVT treatment, despite the potential treatment benefit. Overall, this places further strain on CSCs, patients and relatives.

A recent study in a single EVT-capable centre utilised NCCT and CTA only to triage patients eligible for EVT, regardless of the time window. It demonstrated that patients treated with EVT achieved significantly improved functional independence, without any differences with respect to symptomatic intracranial haemorrhage and mortality, compared with EVT-eligible patients treated with best medical therapy only (management difference was due to limitations in the EVT service hours and capacity during the study period).[13] The reported treatment effect size and the number needed to treat (NNT=3.3) to achieve functional independence at 90 days in this study were comparable to those noted in the DAWN (NNT=2.8) and DEFUSE-3 (NNT=3.6) trials.[3,4,13] Furthermore, the recently presented results of the MR CLEAN-LATE trials revealed a significant treatment effect in favour of EVT treatment compared with patients treated with best medical therapy only, when the eligibility for EVT in the late window was assessed based on the presence of collateral supply (without CT perfusion or MR imaging), despite exclusion of DAWN- or DEFUSE-3-eligible patients from the trial (results presented at the World Stroke Congress 2022).[14] Treatment benefit of EVT was also demonstrated when patients were stratified according to their baseline ASPECTS in the recent AURORA pooled analysis of individual patient data of RCTs that included patients in the late window.[2,15] Numerous other studies have similarly reported comparable functional and safety outcomes between patients assessed to be eligible for EVT using NCCT and CTA only and those using CT perfusion or MR imaging.[12,16] These findings suggest that (i) a proportion of patients who did not meet the DAWN or DEFUSE-3 imaging criteria for EVT eligibility still benefited from EVT treatment compared with best medical therapy only, and (ii) an equally high proportion of 'slow progressors' with a limited infarct core and good collateral supply may be feasibly selected with NCCT and CTA alone, compared with CT perfusion or MR imaging selection, beyond 6 hours from stroke onset. Hence, although the restrictive imaging criteria utilising CT perfusion or MR imaging may lead to a marginally higher likelihood of patients achieving functional independence, the resulting (much) smaller proportion of patients eligible for EVT limits the potential treatment impact on the population as a whole. The increasing use of artificial intelligence software to provide automated infarct volume estimation on NCCT and collateral scoring on CTA has also been useful in aiding the decision-making process and potentially expediting EVT referrals in PSCs and across stroke networks.

Therefore, the future role of CT perfusion and MR imaging in the emergency setting of an acute stroke remains unclear, as it will depend on the logistical context and may change with new insights from ongoing and future studies. It may perhaps be limited to the assessment of eligibility in patients with a borderline ASPECTS or an apparent large infarct core volume at presentation, and in patients with unclear or absent collaterals on CTA. CT perfusion may also be useful in aiding detection and/or selection of patients with a distal medium vessel occlusion who may be eligible for EVT, randomised trials of which are currently ongoing.[17]

Due to evident limitations in the capacity of PSCs to provide comprehensive emergent stroke investigation pathways in the UK, there is a pressing requirement to simplify imaging selection criteria that determine the eligibility for EVT treatment for patients with late-window stroke. Any change should take account of the potentially increased treatment benefit at a population level, the impact on the logistics of stroke workflow in both PSCs and CSCs, as well as the health economics in publicly funded healthcare systems. Current guidelines should be updated expeditiously to reflect the level I evidence in support of more liberal imaging selection criteria for patients presenting with acute ischaemic stroke due to a large vessel occlusion. ■

References

1 Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM *et al*. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723–31.

2 Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J *et al*. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;372:1019–30.

3 Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S *et al*. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018;378:708–18.

4 Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P *et al*. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018;378:11–21.

5 Albers GW. Late window paradox. *Stroke* 2018;49:768–71.

6 Tsivgoulis G, Katsanos AH, Schellinger PD, Köhrmann M, Caso V, Palaiodimou L *et al*. Advanced neuroimaging in stroke patient selection for mechanical thrombectomy. *Stroke* 2018;49:3067–70.

7 Goyal M. Acute stroke intervention results: the "denominator" fallacy. *AJNR Am J Neuroradiol* 2014;35:616–8.

8 Powers WJ, Rabinstein AA, Ackerson T *et al*. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46–e110.

9 Turc G, Bhogal P, Fischer U *et al*. European Stroke Organisation (ESO) – European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischemic stroke. *J Neurointerv Surg*. 2019;neurint-surg-2018-014569.

10 National Institute for Health and Care Excellence. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management. NICE guideline [NG128], updated 2022. www.nice.org.uk/guidance/ng128 [Accessed 21 February 2023].

11 Hargroves D, Lowe D. *GIRFT Programme National Specialty Report 2022*. https://gettingitrightfirsttime.co.uk/medical_specialties/stroke/ [Accessed 21 February 2023].

12 Dhillon PS, Butt W, Podlasek A, McConachie N, Lenthall R, Nair S *et al*. Association between time to treatment and clinical outcomes in endovascular thrombectomy beyond 6 hours without advanced imaging selection. *J Neurointerv Surg* 2022;neurint-surg-2021-018564.

13 Dhillon PS, Butt W, Jovin TG, Podlasek A, McConachie N, Lenthall R *et al*. Endovascular thrombectomy versus best medical therapy for late presentation acute ischemic stroke with proximal large-

vessel occlusion selected on the basis of noncontrast computed tomography: a retrospective analysis of 2 prospectively defined cohorts. *Stroke Vasc Interv Neurol* 2022;0:e000686.
14 Pirson FAVA, Hinsenveld WH, Goldhoorn RB, Staals J, de Ridder IR, van Zwam WH *et al*. MR CLEAN-LATE, a multicenter randomized clinical trial of endovascular treatment of acute ischemic stroke in The Netherlands for late arrivals: study protocol for a randomized controlled trial. *Trials* 2021;22:160.
15 Jovin TG, Nogueira RG, Lansberg MG, Demchuk AM, Martins SO, Mocco J *et al*. Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA): a systematic review and individual patient data meta-analysis. *Lancet* 2022;399:249–58.
16 Nguyen TN, Abdalkader M, Nagel S, Qureshi MM, Ribo M, Caparros F *et al*. Noncontrast computed tomography vs computed tomography perfusion or magnetic resonance imaging selection in late presentation of stroke with large-vessel occlusion. *JAMA Neurol* 2022;79:22–31.
17 Bathla G, Pillenahalli Maheshwarappa R, Soni N, Hayakawa M, Priya S, Samaniego E *et al*. CT perfusion maps improve detection of M2-MCA occlusions in acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2022;31:106473.

Address for correspondence: Dr Permesh Singh Dhillon, Interventional Neuroradiology, Queens Medical Centre, Derby Road, Nottingham University Hospitals NHS Trust, Nottingham, NG7 2UH, UK.
Email: permesh.dhillon@nottingham.ac.uk
Twitter: @PermeshSD