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Current State and Future for Emerging Stroke Therapies: Reflections and Reactions

Keith W Muir

School of Psychology & Neuroscience, University of Glasgow, Queen Elizabeth University Hospital, Glasgow, Scotland, UK.

ORCID: 0000-0001-9535-022X

Keith.muir@glasgow.ac.uk

Gustavo Saposnik

Stroke Outcomes & Decision Neuroscience Unit, Li Ka Shing Institute, University of Toronto, Canada Division of Neurology, Department of Medicine, St. Michael's Hospital, University of Toronto, Canada

<https://orcid.org/0000-0002-5950-9886>

Gustavo.saposnik@unityhealth.to

Correspondence to keith.muir@glasgow.ac.uk

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Surveying the potential emerging therapies for stroke over recent years prompts us to offer some reflections and to consider the challenges faced by researchers developing new treatments. We choose to focus on acute therapies and rehabilitation / recovery treatments as the two main areas that demand stroke-specific solutions, rather than the more clearly defined primary and secondary prevention approaches.

Acute stroke treatment has enjoyed two major successes over the past 30 years, both involving early reperfusion of the ischaemic brain. Both thrombolytic drug treatment and endovascular thrombectomy, after some initial stutters, hit upon successful strategies for patient selection and trial design that yielded a very large treatment effect compared with control groups. The key design elements included a combination of clinical and imaging criteria, specific technologies, and crucially, short onset to treatment time intervals. The large treatment effects meant that sample size for these trials was accordingly small – 624 participants in the NINDS trial¹ and 500 in MR CLEAN² were sufficient to provide highly significant results for clinically robust disability endpoints, and thus compelling evidence of benefit. The current and future challenge for emerging acute therapies is to develop an effective trial strategy in the face of highly effective reperfusion therapies being widely available as standard of care, effect sizes likely to be much smaller, and in light of the consequences of higher life expectancy and the population ageing (e.g. higher burden of comorbidities also leading to higher frailty^{3,4}). How might this be achieved?

Trials can pursue either patients receiving reperfusion therapies, or target those currently ineligible. Pursuing the reperfusion-eligible population faces the prospect of any new treatment being likely to yield only small incremental effects, with attendant substantially increased sample size compared with what has become typical in the stroke field. While cardiology successfully and rapidly evolved networks capable of delivering acute trials including tens of thousands of patients, this relied on simple end-points and selection criteria and it is unclear whether stroke, reliant on advanced imaging to select cases, and complex disability outcomes, will be able to expand capacity in a similar manner. Limited access to specialist stroke care necessitates cooperative networks of centres, but resources at spoke sites are limited, particularly the capacity to prosecute complex research protocols. Recruiting large numbers of patients through a network model is challenging. Acute trials that target those who present via transfer from spoke sites to endovascular centres have hypothesised incremental benefit based on retarding ischaemic tissue damage, or enhancing non-endovascular reperfusion rates.⁵ However, recent experience from direct-to-endovascular treatment trials has highlighted the vulnerability of such studies to ever-shortening workflow time intervals and improved field triage of thrombectomy-eligible patients that redirects them to a comprehensive treatment centre, with smaller than anticipated differences in the interval to endovascular treatment⁶ – and consequently very small magnitude of effect size.

Pre-hospital trials represent another potential target for very early pre-reperfusion interventions, but even for safe and widely available established treatments, the poor sensitivity of clinical criteria for separating ischaemic stroke from haemorrhage from mimics introduces further limitations,⁷ and the need to match field patient selection and treatment initiation with adherence to trial protocols across all destination hospital services is logistically complex. Mobile stroke units that include brain imaging facilities or in-field medical expertise have limited population coverage even where local infrastructure exists.

The great majority of stroke patients remain ineligible for reperfusion treatments, therefore targeting this group for future trials is superficially attractive. The interventional field is already pushing beyond the criteria used in the definitive clinical trials, however, to argue for treatment of groups with lower ASPECT scores, more distal occlusion sites, larger ischaemic core volumes, and

frail patients with prior disability. It is likely that trial-capable centres will have increasing difficulty in finding thrombectomy-ineligible patients as techniques and devices advance, and clinical practice runs ahead of trial evidence to embrace wider populations. In other words, this new standard of care will include more patients eligible for reperfusion therapies, but also narrows their future scope by selecting subgroups with smaller therapeutic margins. The impact on trial recruitment and outcomes is uncertain but is potentially detrimental as the assumptions regarding severity and outcomes may be modified by practice drift.⁸ An alternative strategy is to target less severe stroke – clinically minor, or those without intracranial occlusion amenable to endovascular approaches.⁹ Less severe stroke represents a majority of patients presenting to hospital, so numbers are hypothetically plentiful. Whether current outcome measures are suited to this group is questionable. Already, successive thrombolytic drug trials have witnessed decrementing severity of stroke, and the modified Rankin Scale as the most widely used functional outcome measure offers little discriminatory power when the great majority of trial participants experience excellent recovery (e.g. as seen in NOR-TEST).¹⁰ There is a lack of a universally accepted measure that discriminates different grades of outcome in this situation, although tools that are more meaningful for patients such as the EuroQOL visual analogue scale are promising. Regulatory and general clinical acceptance of an intervention will be anchored in changes in clinically meaningful outcomes.

Imaging will remain a key element of patient selection. The large number of physiologically relevant imaging prognostic measures – including core and penumbra volume, collaterals, occlusion site, indices of tissue damage such as ASPECTS, clot burden score, intracranial haemorrhage volume and location – points towards mandatory minimum imaging to characterise populations and ensure that modest-sized trials can adjust for random variation in disease severity among groups, but carries requirements that include standardisation of selection-critical interpretation and minimum site competencies and technical capacity. For reperfusion therapies, angiographic recanalization / reperfusion grade has already become a technical endpoint, but given the high proportion of patients significantly disabled at day 90 despite optimal endovascular reperfusion being achieved,¹¹ this alone cannot be a viable surrogate. It is unclear whether other imaging endpoints offer biomarkers for functional outcomes. Follow-up infarct volume is widely used in trials but mediates only a small part of the variation in day 90 outcome,¹² and it is unclear whether addressing potentially correctable factors such as variable timing or modality of imaging will improve performance. If instead an imaging biomarker needs to reflect more complex factors such as lesion location, or disruption of functional networks,^{13,14} then substantial investment in newer technologies may be necessary. At present, widely available imaging biomarkers may not reduce sample size compared with clinical measures, and are vulnerable to variation in patient selection strategy.¹⁵ The minimum clinically important difference for an imaging biomarker remains undefined.

Trials in the subacute or recovery stages that investigate restorative or rehabilitation strategies require innovation in trial design to similarly address patient selection strategies and biomarkers but with some specific added issues, and with few exemplars of successful trial strategies to suggest a solution. Vagus nerve stimulation exemplifies several of these.¹⁶ Physical interventions – be they devices, implants, cell injections, or human interactions of one kind or another – are often difficult to blind effectively. Implanted devices may limit imaging options, or necessitate surgical removal at the end of a trial. The mode of action is often complex, ill-defined, and multi-dimensional, making it more difficult to identify relevant biomarkers. Using specific functional impairment endpoints, such as upper limb motor function, imposes specific selection criteria that may narrow patient eligibility, and therefore recruitment, markedly. Any intervention that requires repeated visits, or sustained treatment, is vulnerable to loss of participants, more likely when perceived to be ineffective or tiresome, and causes particular difficulty in interpreting longitudinal performance data when the

participants at each time point are not the same individuals.¹⁷ General functional outcomes such as the mRS are still viewed as suboptimal by rehabilitation specialists,¹⁸ at least for early phase explanatory studies, and trials that target specific neurological impairments remain common, with consequent narrowed eligibility criteria, difficulty in generalising findings to other deficits, and under-representation of patient groups (e.g. visual field loss, visuospatial neglect, frailty) in trials. Identifying a universally agreed minimally important difference, and finding a large enough effect to be detected with a modest sample size, remain elusive goals.

In conclusion, the major advances in acute reperfusion therapies are of major clinical benefit and inform the design of future trials. Continued innovation in trial design is of critical importance to the success of emerging therapies, since the very large effect sizes for reperfusion are unlikely to be replicated and new therapies will be tested on the background of ever-expanding indications for reperfusion. Solutions that may only be amenable for small groups of patients will not necessarily accomplish the main goal: improving the quality of life and clinical outcomes that are meaningful for stroke survivors.

References

1. The National Institute of Neurological Disorders & Stroke Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581-1587.
2. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. *N Engl J Med*. 2015;372:11-20.
3. Palmer K, Vetrano DL, Padua L, Romano V, Rivoiro C, Scelfo B, Marengoni A, Bernabei R, Onder G. Frailty Syndromes in Persons With Cerebrovascular Disease: A Systematic Review and Meta-Analysis. *Front Neurol*. 2019;10:1255.
4. Evans NR, Todd OM, Minhas JS, Fearon P, Harston GW, Mant J, Mead G, Hewitt J, Quinn TJ, Warburton EA. Frailty and cerebrovascular disease: Concepts and clinical implications for stroke medicine. *Int J Stroke*. 2022;17:251-259.
5. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, Yan B, Bush SJ, Dewey HM, Thijs V, et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. *N Engl J Med*. 2018;378:1573-1582. doi:
6. Lobotesis K, Buck BH. Direct to Thrombectomy. *Stroke*. 2021;52:2442-2444.
7. RIGHT-2 Investigators. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. *Lancet*. 2019;393:1009-1020.
8. Alexandrov AV, Tsvigoulis G, Kohrmann M, Katsanos AH, Soinnie L, Barreto AD, Rothlisberger T, Sharma VK, Mikulik R, Muir KW, et al. Endovascular equipoise shift in a phase III randomized clinical trial of sonothrombolysis for acute ischemic stroke. *Ther Adv Neurol Disord*. 2019;12:1756286419860652.
9. Lau HL, Gardener H, Coutts SB, Saini V, Field TS, Dowlathshahi D, Smith EE, Hill MD, Romano JG, Demchuk AM, et al. Radiographic Characteristics of Mild Ischemic Stroke Patients With Visible Intracranial Occlusion: The INTERRSeCT Study. *Stroke*. 2022;53:913-920.
10. Logallo N, Novotny V, Assmus J, Kvistad CE, Altehheld L, Ronning OM, Thommessen B, Amthor KF, Ihle-Hansen H, Kurz M, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol*. 2017;16:781-788.
11. Liebeskind DS, Bracard S, Guillemin F, Jahan R, Jovin TG, Majoie CB, Mitchell PJ, van der Lugt A, Menon BK, San Roman L, et al. eTICI reperfusion: defining success in endovascular stroke therapy. *J Neurointerv Surg*. 2019;11:433-438.
12. Boers AMM, Jansen IGH, Brown S, Lingsma HF, Beenen LFM, Devlin TG, Roman LS, Heo JH, Ribo M, Almekhlafi MA, et al. Mediation of the Relationship Between Endovascular Therapy and Functional Outcome by Follow-up Infarct Volume in Patients With Acute Ischemic Stroke. *JAMA Neurol*. 2019;76:194-202.
13. Schlemm E, Ingwersen T, Konigsberg A, Boutitie F, Ebinger M, Endres M, Fiebach JB, Fiehler J, Galinovic I, Lemmens R, et al. Preserved structural connectivity mediates the clinical effect of thrombolysis in patients with anterior-circulation stroke. *Nat Commun*. 2021;12:2590.
14. Konigsberg A, DeMarco AT, Mayer C, Wouters A, Schlemm E, Ebinger M, Cho TH, Endres M, Fiebach JB, Fiehler J, et al. Influence of stroke infarct location on quality of life assessed in a multivariate lesion-symptom mapping study. *Sci Rep*. 2021;11:13490.
15. Campbell BCV, Lansberg MG, Broderick JP, Derdeyn CP, Khatri P, Sarraj A, Saver JL, Vagal A, Albers GW, Consortium SX. Acute Stroke Imaging Research Roadmap IV: Imaging Selection and Outcomes in Acute Stroke Clinical Trials and Practice. *Stroke*. 2021;52:2723-2733.
16. Dawson J, Liu CY, Francisco GE, Cramer SC, Wolf SL, Dixit A, Alexander J, Ali R, Brown BL, Feng W, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor

function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. *Lancet*. 2021;397:1545-1553.

17. Dromerick AW, Geed S, Barth J, Brady K, Giannetti ML, Mitchell A, Edwardson MA, Tan MT, Zhou Y, Newport EL, et al. Critical Period After Stroke Study (CPASS): A phase II clinical trial testing an optimal time for motor recovery after stroke in humans. *Proc Natl Acad Sci U S A*. 2021;118:e2026676118.
18. Kwakkel G, Lannin NA, Borschmann K, English C, Ali M, Churilov L, Saposnik G, Winstein C, van Wegen EE, Wolf SL, et al. Standardized measurement of sensorimotor recovery in stroke trials: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. *Int J Stroke*. 2017;12:451-461.