assess whether the new intervention results in similar, if not better-quality, faster, and safer reperfusion. Without this assessment, we risk the effect of bio-creep, where a slightly inferior treatment becomes the comparator for the next generation of trials, ultimately leading to degradation of the efficacy of the intervention.[12] However, we think the direct aspiration as first-pass technique in the COMPASS trial did indeed pass this test.

Whether the results of the COMPASS trial should change practice is a difficult question to answer. Neurointervention is dependent on the specialised skillset of the operator; different operators might learn, adopt, and feel comfortable with different techniques. Neurointerventionists should, however, constantly measure their procedural outcomes (ie, speed, efficacy, and safety of reperfusion) against current benchmarks.[3–5] Seen this way, the COMPASS trial offers another evidence-based approach to endovascular thrombectomy that might be used to complement or improve techniques when compared with benchmark data.

*Bijoy K Menon, *Mayank Goyal*
Calgary Stroke Program, Departments of Clinical Neurosciences, Radiology (BKM, MG), and Department of Community Health Sciences (BKM), Cumming School of Medicine, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada; and Seaman Family MR Research Centre, Foothills Medical Centre, Calgary, AB T2N 2T9, Canada (MG)
mgoyal@ucalgary.ca

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Considering prehospital stroke trials: did RIGHT-2 get it right?

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Hypertension at the time of first assessment in stroke is common and associated with poor outcome.[1,2] Previous clinical trials have shown that lowering of blood pressure in the first 24 h of ischaemic stroke[3] and in the first 6 h in intracerebral haemorrhage[4,5] does not improve outcomes in these populations. The RIGHT-2 study[6] in *The Lancet* was a multicentre, ambulance-based, randomised, sham-controlled, phase 3 trial with masked outcome assessment designed to assess the safety and efficacy of transdermal glyceryl trinitrate (GTN), a nitric oxide donor, in a hyperacute stroke population. The primary outcome was the 7-level modified Rankin Scale (mRS; a measure of functional outcome) at 90 days, assessed by central telephone follow-up with masking to treatment. The investigators enrolled a total of 1149 patients (mean age 72·5 years; 48% women) and found no improved outcome in the GTN group compared with the sham group in cohort 1 (patients with stroke or transient ischaemic attack; adjusted common odds ratio [acOR] 1·25 [95% CI 0·97–1·60];

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p=0·083) or in cohort 2 (all patients—ie, intention to treat [ITT]; 1·04 [0·84–1·29]; p=0·69). No difference was found between the two groups in deaths at day 4 in either cohort (cohort 1: acOR 1·17 [0·57–2·39]; p=0·68; cohort 1: 1·19 [0·60–2·35]; p=0·63). Additional analyses suggested potential harm, with worse outcomes in patients with intracerebral haemorrhage (p=0·057), the earliest enrolled (<1 h) patients (p=0·014), and the most severe strokes (National Institutes of Health Stroke Scale >12; 0·044). We believe the clinical community now has data from numerous populations suggesting that blood pressure lowering in the acute and hyperacute setting is not beneficial to patients with stroke.

Although the intervention did not improve clinical outcome, prehospital treatment with GTN used 184 ambulance stations in eight ambulances services in England and Wales as the trial sites, and 516 paramedics as the front-line recruiting investigators. This trial[6] is the first in the UK to our knowledge to show the ability of the emergency medical service teams to successfully enrol in a hyperacute stroke clinical trial in the field. The FAST-MAG trial[7] in the USA has previously shown such a model, with the enrolment of 1700 patients in a phase 3 trial assessing magnesium (4 g intravenous magnesium sulphate) in acute stroke in the Los Angeles area. Such trials are changing the paradigm of acute stroke research by showing the feasibility of very early treatment initiation within a median of 45 min for FAST-MAG[7] and 73 min for RIGHT-2.[6]

The limitations of a prehospital enrolment model are also shown in RIGHT-2. This trial had an original sample size of 850 patients (425 per group), which provided 90% power to detect an ordinal shift in the mRS. This sample size took into account a 3% loss to follow-up and a 20% stroke mimic rate. During the trial, the non-stroke diagnosis rate exceeded 30% in patients who were randomly assigned, therefore reducing the power to assess the efficacy of the intervention in the target population. Thus, the sample size was increased to 1050 to maintain statistical power at the predefined clinically relevant difference. Additionally, a decision was made by the trial steering committee to specify a hierarchical analysis with the first analysis of patients with stroke or transient ischaemic attack (cohort 1) and the second analysis of all patients (the ITT population; cohort 2), which presumably was the primary analysis population initially. The final study population (n=1149; cohort 1, n=852) included 52% with ischaemic stroke, 13% intracerebral haemorrhage, 9% transient ischaemic attack, and 26% stroke mimics. The RIGHT-2 investigators stated that they did not expect the treatment to benefit non-stroke patients but acknowledged that this population would be enrolled and treated under the current design. Although cohort 1 primary analysis addresses this high mimic rate, future prehospital trials need to consider the implications of enrolling, yet excluding, stroke mimics in the primary analysis. Incorporation of additional features, similar to what was done in FAST-MAG,[7] might help avoid a high stroke mimic rate. FAST-MAG had 73% of patients with ischaemic stroke and 23% of patients with haemorrhagic stroke with only a 4% stroke mimic rate. The trial design used a physician on the telephone with the emergency medical teams at the time of enrolment.[7] The use of telemedicine techniques in the ambulance to bring the stroke provider into direct contact with the patient and emergency medical services provider might be another approach in clinical trials to reduce enrolment of mimics.[8] Early data suggest reliability of technology[9] and accurate stroke diagnosis,[10] although further research is needed. Improved tools to exclude stroke mimics in the field have been difficult to develop and validate.[11] The absence of imaging in most ambulances will continue to limit field personnel from definitively determining ischaemic stroke from intracerebral haemorrhage, which will limit hyperacute trials to interventions presumed safe in both populations.

In addition to design aspects, a key element in the interpretation of the results of RIGHT-2[6] is the effect of the intervention on blood pressure, as measured by the separation between the two treatment groups. Systolic blood pressure was lower in the GTN group than the sham group by 5·8 mm Hg after initial treatment, and diastolic blood pressure was lower by 2·6 mm Hg; at day 2, systolic blood pressure was lower by 5·3 mm Hg and diastolic by 2·6 mm Hg in the GTN group compared with the sham group. However, these differences between groups in blood pressure might not be considered clinically relevant in this setting. The ATACH-2[4] and Interact-2[5] studies showed a 12–14 mm Hg systolic blood pressure difference between treatment groups, although they also did not show benefit in the patients with intracerebral haemorrhage. Additionally, the RIGHT-2 investigators

report no difference in blood pressure at day 3 or day 4 of treatment, which might have been related to the very low adherence to study protocol by day 4 (45% in cohort 1; 36% in cohort 2).

Regardless of these limitations, RIGHT-2 has provided high-level evidence that GTN given within 4 h of onset does not significantly improve outcome in hyperacute patients presenting with possible stroke. Additionally, the trial has added to the existing data that show that future hyperacute treatment trials can successfully offer study treatment in the prehospital setting.

*Karen C Johnston, Valerie L Durkalski-Mauldin
Department of Neurology, University of Virginia, Charlottesville, VA 22911, USA (KCJ); and Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA (VLD-M)
kj4v@virginia.edu

We declare no competing interests.

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Minimally invasive surgery plus alteplase for intracerebral haemorrhage

Stroke has become the second largest contributor to disability-adjusted life-years (DALYs) lost globally.[1] Because of the severity of haemorrhagic stroke, particularly as a result of intracerebral haemorrhage, this condition accounts for more DALYs lost than ischaemic stroke.[1] Despite more than 100 randomised trials[2] assessing various treatments, organised stroke unit care remains the mainstay of therapy to improve outcome after intracerebral haemorrhage.[3,4]

Haemorrhage removal or limitation of early haemorrhage expansion are logical therapeutic targets because of the strong association between intracerebral haemorrhage volume and poor clinical outcome.

Neurosurgical interventions can reduce the volume of a patient's intracerebral haemorrhage, but it has been difficult to interpret the evidence supporting their clinical effectiveness. On the one hand, a meta-analysis[5] of randomised trials of neurosurgical evacuation of supratentorial intracerebral haemorrhage found a reduction in so-called unfavourable outcomes. On the other hand, the design, risk of bias, and results of these trials varied considerably, and the two largest randomised trials,[5,6] which used mostly craniotomy, yielded neutral results. Consequently, subsequent clinical trials have focused on techniques such as endoscopic evacuation and minimally invasive stereotactic aspiration.

For more than two decades, some participants in randomised trials of minimally invasive aspiration of intracerebral haemorrhage have also received repeated instillation of a thrombolytic drug via a catheter to improve haemorrhage evacuation and clinical outcome.[7,8] In three small randomised trials[9–11] involving a total of 553 participants, minimally invasive surgery with instillation of urokinase reduced the volume of haemorrhage but did not reduce the risk of death, although it might have improved functional outcome. The subsequent minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE) phase 2 trial[12] recruited 96 participants and did


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