HERMES: messenger for stroke interventional treatment

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The treatment approach for acute ischaemic stroke is straightforward: restore blood flow as soon as possible and do it as safely and completely as possible. The overlong path to confirming this simple and intuitive treatment plan leads to the HERMES collaboration, the meta-analysis from Mayank Goyal and colleagues—including principal investigators from the selected trials—published in *The Lancet,* which combines individual patient data from five trials of endovascular mechanical thrombectomy published in 2015.[1]

Data from the 1287 patients (634 assigned to endovascular thrombectomy, 653 assigned to standard care) allowed more precise estimates of overall treatment effect (adjusted common odds ratio for reduced disability 2·49, 95% CI 1·76–3·53; p<0·0001and absence of heterogeneity strengthened conclusions about the consistency of effects across major subgroups of age and severity. The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on the modified Rankin Scale (mRS) for one patient was 2·6, which is extraordinary in itself and a huge advance in care for patients with stroke caused by occlusion of the major intracranial carotid-territory vessels, who often respond poorly to optimal medical care with intravenous thrombolytic drugs[2] and have high risk of mortality or disability. Updates to European and North American guidelines[3–5] for acute stroke management have already reflected the findings of these trials by recommending endovascular thrombectomy in suitable patients, conclusions supported by the HERMES analysis.

The collaborators justifiably omitted earlier trials (most notably IMS-3)[6] since these trials were done in an era when CT angiography was not widely available to confirm arterial occlusion and interventions relied on first-generation thrombectomy devices that were subsequently established as less effective and potentially more hazardous than the stent-retriever devices used in most of the trials in HERMES.[7,8] 71% are reported to have achieved revascularisation—a standard achievable in expert units using the current generation of endovascular thrombectomy devices. However, clinical success cannot be assumed because of revascularisation rates and new technology alone.[9] Replicating the highly efficient networks of care in these trials, exemplified by the very short median time from symptom onset to intravenous thrombolysis of 100 mins, will be a major challenge for many health-care systems.

The individual patient data meta-analysis approach glosses over differences among the component trials that were arguably more evident in group-level meta-analyses.[10] Outcomes in the control groups were markedly different across the five individual trials (mortality ranged from 12% to 22%; excellent functional recovery [defined by mRS scores of 0–1] ranged from 6% to 28%), suggesting that either the application of stated inclusion and exclusion criteria resulted by chance in very different patient selection across trials, or, more likely, that other non-protocol factors influenced patient selection. The potential for additional, uncharacterised, selection biases reflects the circumstances of the trials, which were predominantly done by small numbers of expert, high-throughput, neuroscience-based stroke centres and in a very select group of patients (screening data from one trial[11] suggest that only 1% of stroke patients were included, and around 7% of those eligible for intravenous recombinant tissue plasminogen activator). About a third of patients were transferred to trial neurovascular centres from primary stroke centres (after initiation of intravenous alteplase), and criteria that determined these patient transfer decisions are not described.

Additional selection with perfusion imaging or collateral imaging (as in three of the five HERMES trials) maximises trial efficiency by focusing on patient groups with the greatest likelihood of benefit, but inevitably leads to a larger estimate of absolute treatment effect (and thus a lower number

needed to treat) than if treatment were given to less rigorously selected patients. The potential for imaging selection to exclude patients at very high risk of poor outcome is suggested by two of the three trials reporting reduced mortality by 9–11% in patients assigned to endovascular thrombectomy [11,12] an effect not evident in the pooled analysis. The role for additional perfusion or collateral vessel imaging, and comparison of these different approaches, requires further research, as does the interaction with extensive early ischaemic features on routine CT brain imaging (only 121 patients had an ASPECT score 0–5, signifying more extensive early ischaemic change). Absolute treatment effects will ultimately define the cost-effectiveness of the intervention, and robust cost-effectiveness modelling is required, including set-up costs for countries without the infrastructure for delivery of endovascular thrombectomy. Establishing broad applicability, and characterising the absolute treatment effects in wider populations, will necessitate systematic collection of registry data.

Subgroup definitions are constrained by the original trial selection criteria and framed to ensure reasonable sample size, but several clinically important areas are under-represented in HERMES. Although older patients were better represented in the analysis than in previous acute stroke trials, only 15% were 80 years of age or older. The same proportion had contraindications to intravenous thrombolysis, but this is a broad and undefined group. The trials covered only a very narrow range of onset-to-treatment time, irrespective of protocols (only 208 patients were randomised later than 5 h from onset, and only 69 patients beyond 6 h). In subgroup analyses, lack of statistical heterogeneity is not the same as evidence of efficacy when many major subgroups are so small; implementation of endovascular thrombectomy in circumstances such as late presentation, extensive early ischaemic change on CT, or ineligibility for intravenous recombinant tissue plasminogen activator should be done with caution, and ideally supported in due course by further trial evidence. The benefit of endovascular thrombectomy in more distal anterior circulation vessels (middle cerebral artery segment M2 and beyond) and in the posterior circulation remain unproven. Questions regarding technical issues such as whether general anaesthesia or sedation should be used as the primary approach, the place for aspiration techniques, need for balloon-guiding catheter, adjunctive stenting of coexisting carotid stenosis, or the need for additional intra-arterial thrombolytic drugs, remain unanswered.

Preliminary results of two further trials of endovascular thrombectomy (THRACE [NCT01062698] and THERAPY [NCT01429350]) have been presented, while a third (PISTE [NCT01745692]) will be presented soon.[13] All three trials were stopped prematurely after interim review triggered by the results from the HERMES trials. These unpublished trials include a further 587 patients, predominantly treated with stent retrievers and within similar timelines. It remains to be seen whether results will modify the HERMES collaborators' conclusions about effect size and extend knowledge of subgroups. Nonetheless, the efficacy of endovascular thrombectomy in patients with anterior circulation stroke due to large artery occlusion is established, and implementation should be the priority. Further trials are needed to clarify the boundaries of treatment.

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References

1 Mayank Goyal, Bijoy K Menon, Wim H van Zwam, et al, for the HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016; published online Feb 18. http://dx.doi.org/10.1016/S0140-6736(16)00163-X.
2 Bhatia R, Hill MD, Shobha N, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. *Stroke* 2010; **41:** 2254–58.
3 Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2015; **46:** 3020–35.
4 Wahlgren N, Moreira T, Michel P, et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. *Int J Stroke* 2016; **11:** 134–47.
5 Casaubon LK, Boulanger JM, Blacquiere D, et al. Canadian Stroke Best Practice Recommendations: Hyperacute Stroke Care Guidelines, Update 2015. *Int J Stroke* 2015; **10:** 924–40.
6 Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med* 2013; **368:** 893–903.
7 Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet* 2012; **380:** 1241–49.
8 Nogueira RG, Lutsep HL, Gupta R, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet* 2012; **380:** 1231–40.
9 The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke* 2009; **40:** 2761–68.
10 Badhiwala JH, Nassiri F, Alhazzani W, et al. Endovascular thrombectomy for acute ischemic stroke: a meta-analysis. *JAMA* 2015; **314**: 1832–43.
11 Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015; **372:** 1009–18.
12 Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015; **372:** 1019–30.
13 Khatri P, Hacke W, Fiehler J, et al. State of acute endovascular therapy: report from the 12th thrombolysis, thrombectomy, and acute stroke therapy conference. *Stroke* 2015; **46:** 1727–34.