Endovascular thrombectomy with or without thrombolysis bridging in patients with acute ischaemic stroke: protocol for a systematic review, meta-analysis of randomised trials and cost-effectiveness analysis

Rami Z Morsi,1,2 Yuan Zhang,2 Julián Carrió-Penagos,1 Harsh Desai,1 Elie Tannous 3,4 Sachin Kothari,1 Assem M Khamis 4,5 Andrea J Darzi 2,5 Ammar Tarabichi,1 Reena Bastin,1 Layal Hneiny,5 Sonam Thind,6 Elisheva Coleman,1 James R Brorson,1 Scott Mendelson,1 Ali Mansour,1 Shyam Prabhakaran,1 Tareq Kass-Hout1,6

ABSTRACT

Introduction Current published guidelines and meta-analyses comparing endovascular thrombectomy (EVT) alone versus EVT with bridging intravenous thrombolysis (IVT) suggest that EVT alone is non-inferior to EVT with bridging thrombolysis in achieving favourable functional outcome. Because of this controversy, we aimed to systematically update the evidence and meta-analyse data from randomised trials comparing EVT alone versus EVT with bridging thrombolysis, and performed an economic evaluation comparing both strategies.

Methods and analysis We will conduct a systematic review of randomised controlled trials comparing EVT with or without bridging thrombolysis in patients presenting with large vessel occlusions. We will identify eligible studies by systematically searching the following databases from inception without any language restrictions: MEDLINE (through Ovid), Embase and the Cochrane Library. The following criteria will be used to assess eligibility for inclusion: (1) adult patients ≥18 years old; (2) randomised patients to EVT alone or to EVT with IVT; and (3) measured outcomes, including functional outcomes, at least 90 days after randomisation. Pairs of reviewers will independently screen the identified articles, extract information and assess the risk of bias of eligible studies. We will use the Cochrane Risk-of-Bias tool to evaluate risk of bias. We will also use the Grading of Recommendations, Assessment, Development and Evaluation approach to assess the certainty in evidence for each outcome. We will then perform an economic evaluation based on the extracted data.

Ethics and dissemination This systematic review will not require a research ethics approval because no confidential patient data will be used. We will disseminate our findings by publishing the results in a peer-reviewed journal and via presentation at conferences.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The broad study eligibility criteria will increase the generalisability of our results.
⇒ We will use the Grading of Recommendations, Assessment, Development and Evaluation approach to assess the certainty in evidence for each outcome.
⇒ We will perform an economic evaluation based on the meta-analysed data to assess which treatment strategy is more cost-effective, and we will rank the treatment strategies based on efficacy, safety and cost-effectiveness.
⇒ Our results will be limited by the primary data, for which careful appraisal of the study quality will be carried out.

INTRODUCTION

Intravenous thrombolysis (IVT) has been a long-standing, evidence-based treatment approach for acute ischaemic stroke.1 2 However, IVT must be delivered within 4.5 hours, has many contraindications, may not provide adequate reperfusion, especially in patients with large vessel occlusions, and may even increase the risk of intracranial haemorrhage.3 As such, trials were conducted to evaluate the use of endovascular therapy in patients with acute ischaemic stroke. The Interventional Management of Stroke (IMS) III was a randomised controlled trial (RCT) comparing endovascular therapy after IVT with IVT alone. Endovascular therapy included a variety of techniques, such as mechanical and aspiration thrombectomy,
sten-retriever technology or intra-arterial thrombolysis. The Local Versus Systemic Thrombolysis for Acute Ischaemic Stroke (SYNTHESIS) trial compared endovascular therapy, including intra-arterial thrombolysis, clot disruption or retrieval or a combination of these approaches, with IVT alone. The Mechanical Retrieval and Recanalisation of Stroke Clots Using Embolectomy (MR RESCUE) trial compared patients who underwent endovascular therapy alone versus those who received standard care. These three RCTs all failed to show any benefit for endovascular therapy in acute ischaemic stroke. There were several limitations in these trials, ranging from inconsistencies with imaging selection, timing variables and device use.

Since 2015, several RCTs have shown robust evidence supporting the use of endovascular therapy in patients who present with an acute ischaemic stroke secondary to a large vessel occlusion. Because IVT does not adequately recanalise large or proximal intracranial occlusions, the significant treatment effect of endovascular thrombectomy (EVT) in both IVT-eligible and IVT-ineligible patients with large vessel occlusions, the potential delaying effect of IVT to initiation of EVT and its possible association with increased bleeding events, many RCTs and post hoc analyses of RCTs have evaluated the safety and efficacy of EVT alone versus bridging IVT prior to EVT in patients presenting with acute ischaemic stroke secondary to a large vessel occlusion, and have shown conflicting evidence whether EVT alone would be non-inferior to EVT with pretreatment IVT. The 2019 European Stroke Organisation (ESO)–European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines found high quality of evidence recommending the use of EVT and best medical management within 6 hours after symptom onset, and moderate quality of evidence for use of EVT and best medical management in patients presenting within the window of 6–24 hours. The ESO-ESMINT guidelines published an expedited recommendation strongly recommending IVT plus EVT over EVT alone. Similarly, the 2019 American Heart Association guidelines provided a class I recommendation for the use of IVT prior to EVT in IVT-eligible patients.

There are several published systematic reviews exploring the efficacy of bridging IVT prior to EVT compared with EVT alone; however, they do not adequately assess risk of bias or the certainty of evidence in each outcome, and vary in their study inclusion criteria and methodology. A recently published systematic review and meta-analysis has focused on comparing the two treatment strategies in patients presenting with large vessel occlusions involving only the anterior circulation and has assessed the certainty of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. This review, however, excludes patients with large vessel occlusions in the posterior circulation. None of these systematic reviews consistently assessed the overall certainty of evidence and conducted a cost-effectiveness analysis comparing bridging IVT prior to EVT versus EVT alone. Thus, we propose to conduct a systematic review and meta-analysis of randomised trials to assess the comparative efficacy and safety of EVT alone versus IVT plus EVT for patients with acute ischaemic stroke secondary to large vessel occlusion and perform a cost-effectiveness analysis using the meta-analysed data.

**METHODS AND ANALYSIS**

**Standardised reporting and registration**

We ensured our protocol was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols checklist. This systematic review is registered with International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42022315608).

**Eligibility criteria**

We will include randomised trials meeting the following criteria: (1) enrolled adult patients ≥18 years old presenting with an acute ischaemic stroke secondary to a large vessel occlusion, regardless of vessel involved, and (2) randomised patients to undergo EVT alone or to receive IVT in addition to EVT. We will include trials that permitted cointerventions (eg, intra-arterial thrombolysis, rescue stenting) only if the same cointerventions were used in patients from all study arms. Table 1 provides a more detailed representation of the inclusion and exclusion criteria.

**Data sources and search strategy**

An information specialist (LH) developed the search strategy for the databases (figure 1, online supplemental appendix 1). We will conduct our searches systematically looking for eligible studies in MEDLINE (through Ovid), Embase and the Cochrane Library from inception without language restrictions. We will also review the reference lists of included studies and relevant reviews to identify any additional studies meeting the eligibility criteria.

**Study selection**

Prior to the screening process, teams of two reviewers will participate in calibration exercises. Following the calibration exercises, teams of two reviewers will subsequently double screen the titles and abstracts of all identified citations. These pairs of two reviewers will then retrieve and double screen the full texts of all citations for eligibility.

**Data extraction**

We designed a standardised extraction form and a comprehensive instruction manual to assist with data extraction. We will conduct calibration exercises prior to the data extraction phase to ensure accuracy and consistency.
Pairs of two reviewers will subsequently extract data independently and review in duplicate.

Reviewers will extract the following data for all included studies: study characteristics (eg, author information, country of origin and study design), patient characteristics (eg, sample size, age and sex of patients, medical history, National Institute of Health Stroke Scale score, the proportion for each vessel involved as well as determined stroke aetiology), characteristics of interventions and comparators (eg, intravenous thrombolytic agent used and respective dose and thrombectomy device used) and treatment outcomes, including mortality, functional independence, successful reperfusion, intracranial haemorrhage (including symptomatic intracranial haemorrhage), and procedural complications and other adverse events. Data will be abstracted into an Excel spreadsheet using Microsoft Office Excel V.2021. If there are any missing details, we will contact the authors of included studies when applicable.

We conducted a preliminary literature search of the databases, and conclusion of the search suggests that there will be an estimate of six studies eligible for this review.

### Risk of bias assessment

Pairs of reviewers will assess the risk of bias of included studies independently and in duplicate using the revised Cochrane Risk-of-Bias V.2 (RoB 2) tool. We will address concerns for low interrater reliability and other expected challenges, such as difficult terminology, by training the reviewers to improve the reliability of RoB 2. We will use the following criteria to assess risk of bias: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. We will resolve any disagreements between reviewers through consensus and/or with the assistance of an adjudicator. Risk of bias for included studies will be illustrated in figures produced by Risk-of-bias Visualization.

### Data synthesis

We will group all outcomes reported by at least two studies for direct comparison. We will standardise the definitions and measurements of each outcome via consensus. We will conduct a meta-analysis of the outcomes of interest when possible using the generic inverse variance method and random effects analysis model via Review Manager V.5.4. We will use Harbord’s test to assess small study effects for binary outcomes and Egger’s test for continuous outcomes when there are at least 10 studies eligible for quantitative assessment. When no meta-analysis could be performed due to heterogeneity of the data, we will narratively synthesise the findings. For dichotomous outcomes reported by at least one RCT, we will calculate the relative risk (RR) using the crude event rate and the associated 95% CIs to inform relative effectiveness. We will calculate risk difference based on the RRs from our study and the baseline risks from a well-designed, high-quality multicentre observational study of 6350 patients who had ischaemic stroke. For continuous outcomes reported by at least one RCT, we will calculate the weighted mean difference and associated 95% CI. When only median and range values are reported or when SD are not reported, we will use methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions and by Wan et al to estimate means and SD. We will report our synthesised findings as funnel plots to assess for asymmetry per outcome of interest and will also estimate Egger’s test of the intercept to assess for publication bias.

### Subgroup analysis

We will evaluate statistical heterogeneity using inconsistency measures, Cochrane’s Q test and I². We will use the following a priori hypotheses to explain heterogeneity...
between studies: (1) location of vessel involved (eg, anterior circulation or posterior circulation) will show different treatment effects54; (2) high risk of bias studies will show larger treatment effects; and (3) type of thrombectomy devices used (eg, stent retriever, aspiration, etc). We will perform subgroup analyses irrespective of the heterogeneity estimates as long as there are at least two studies representing each subgroup.

Assessing certainty of the evidence
For each outcome, we will assess the certainty of the evidence (as high, moderate, low or very low) using the GRADE approach and developed GRADE evidence profiles.55, 56 We will use previously derived thresholds for the minimally important difference for favourable functional outcome, mortality and symptomatic intracranial hemorrhage (sICH), adapted from Wang and colleagues.57

Cost–utility analysis
We will conduct a model-based cost–utility analysis to determine the cost-effectiveness of EVT alone compared with IVT and EVT for patients with an acute ischaemic stroke secondary to a large vessel occlusion. A Markov decision analytical model with a lifetime horizon will...
be developed to predict the long-term costs and health outcomes. We will conduct the analysis from a health-care perspective. We will base the clinical outcome inputs from this systematic review. We will search literature for the long-term clinical outcome inputs. From the health-care perspective, we will consider both medical costs (ie, costs related to patient care) and non-medical costs (ie, overhead costs such as finance, human resources and administration) that are incurred during treatment. The treatment costs come from the administrative data of the University of Chicago Medical Center. Other cost estimates (ie, health state-related costs) and utility inputs will be based on literature.

Patient and public involvement
Neither patients nor the public was involved in the study.

Ethics and dissemination
This systematic review will not require a research ethics approval because no confidential patient data will be used. We will disseminate our findings by publishing the results in a peer-reviewed journal and via presentation at conferences.

DISCUSSION
EVT has emerged to become a superior treatment modality compared with medical management alone for the treatment of strokes secondary to large vessel occlusions, particularly in the anterior circulation. However, controversies in the safety and efficacy of bridging IVT prior to thrombectomy remain to be the subject of debate. A recent subgroup analysis showed that the effect of intravenous alteplase prior to thrombectomy is not significantly associated with the occlusion site, however, the trial for which this analysis was based included only occlusions in the internal carotid and M1 or M2 branches of the middle cerebral artery. An editorial by Podlasek and colleagues briefly reviewed the combined the trial data from six RCTs and showed that EVT alone is non-inferior to bridging therapy in achieving good functional outcomes at 3 months with a 6% margin of confidence. While most guidelines currently recommend IVT prior to thrombectomy, there is a need for a high-quality review to provide a clinical summary of the efficacy and safety of mechanical thrombectomy alone versus EVT prior to mechanical thrombectomy and to balance those outcomes with cost.

Our study will have many strengths compared with existing reviews in the literature. First, we will compare the efficacy and safety of mechanical thrombectomy alone versus mechanical thrombectomy and bridging thrombolysis in studies that only directly compare the two interventions strategies. Second, we will investigate the effects of treatment across certain conditions. Third, we will apply the RoB 2 tool and GRADE approach to evaluate the risk of bias and certainty of evidence, respectively, for each outcome. Lastly, this study will be the first to use meta-analysed data to robustly perform an economic evaluation comparing the two treatment strategies, integrate clinical outcome inputs from study-level data and treatment cost inputs from administrative data. Some potential limitations will include the following: heterogeneity of outcome definitions and measurement, such as in the case of symptomatic intracranial haemorrhage; cost estimation cannot assess for lifetime cost as there are limited longitudinal data with respect to the treatment strategies. The findings of our study will help inform providers about the role of IVT in mechanical thrombectomy and identify key areas for future research.

Author affiliations
1Department of Neurology, University of Chicago, Chicago, Illinois, USA
2Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
3Department of Pathology, Albany Medical Center, Albany, New York, USA
4Wolfson Palliative Care Research Centre, Hull York Medical School, Hull, UK
5Wegner Health Sciences Information Center, University of South Dakota, Sioux Falls, South Dakota, USA
6Section of Neurosurgery, Department of Surgery, University of Chicago, Chicago, Illinois, USA

Twitter Loyal Hneiny @LHneiny

Contributors RZM and TK: conception and design of the work, analysis, drafting of the manuscript and final approval. YZ, AMK and AJD: analysis, design of the work and drafting of the manuscript and final approval. JC-P, HD, ET, SK, AT and RB: data collection. LH: design of the work and final approval. ST, EC, JRB, SM, AM and SP: analysis, drafting of the work and final approval. All authors reviewed and contributed to the final version of this article.

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ORCID iDs
Rami Z Morsi http://orcid.org/0000-0003-2131-3711
Elie Tannous http://orcid.org/0000-0002-1975-190X
Assem M Khamis http://orcid.org/0000-0002-5567-7065
Andrea J Darzi http://orcid.org/0000-0002-2498-1697

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