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Stenting versus medical therapy alone for symptomatic intracranial arterial stenosis: protocol for a systematic review and individual patient data meta-analysis

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ABSTRACT

Introduction Intracranial atherosclerotic stenosis (ICAS) is a common cause of stroke worldwide. However, whether the treatment options for symptomatic ICAS is stent placement or medical therapy alone is still controversial. At present, three multicentre randomised controlled trials (RCTs) have been published, but their research designs are also slightly different and the conclusions are not completely consistent. Therefore, we plan to conduct a systematic review and individual patient data (IPD) meta-analysis of randomised clinical trials to ascertain safety and efficacy of stenting versus medical therapy alone for symptomatic patients with intracranial arterial stenosis.

Methods and analyses We will identify RCTs comparing stenting vs medical therapy alone in patients with symptomatic ICAS stenosis (70%–99%) through a systematic search, mainly including PubMed, MEDLINE, EMBASE, the Cochrane Library and ClinicalTrials.gov. Individual-level patient data for a prespecified list of variables will be sought from authors of all eligible studies. The primary outcome was a composite of stroke or death within 30 days, or stroke in territory of qualifying artery beyond 30 days after randomisation. IPD meta-analysis will be conducted with a one-stage approach.

Ethics and dissemination Ethical approval and individual patient consent will not be required in most cases since this IPD meta-analysis will use pseudonymised data from RCTs. Results will be disseminated through peer-reviewed journals and international conferences.

PROSPERO registration number CRD42022369922.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Individual patient data (IPD) meta-analysis will provide larger sample size with higher statistical power and precision, possibility to adjust for multiple confounding factors, perform meaningful subgroup analysis and more advantages.

⇒ IPD meta-analyses are limited by available data, which may limit the number of included studies and thus limit generalisability.

⇒ Additionally, there may be inconsistencies in how covariates are reported, limiting the number of variables that can be included in the analysis.

⇒ A potential limitation is the long time span of the studies planned for inclusion in the analyses.

INTRODUCTION

Intracranial atherosclerotic stenosis (ICAS), also known as intracranial atherosclerotic disease (ICAD), is a common cause of stroke worldwide.1,2 ICAS accounted for 5%–10% of the causes of stroke in Caucasians, 15%–29% of transient ischaemic attack (TIA) or stroke in blacks, and up to 30%–50% of the causes of stroke in Asians.3 The American Heart Association/American Stroke Association guidelines for secondary prevention of stroke and TIA in 2021 recommended medical therapy as the first-line treatment for ICAS.4 However, studies have found that the rates of any stroke or death at 1 year in symptomatic ICAS patients was as high as 7.2%–17.5% even with intensive medical therapy.5,6

Endovascular therapy is an effective alternative, especially for patients refractory to medical treatment and in the Asian population with a high incidence of ICAS.7 For the endovascular treatment of symptomatic ICAS, although the Stenting vs Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)8 and the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT)8 trials did not show the advantages of endovascular treatment compared with medical therapy, post hoc analysis of the SAMMPRIS and VISSIT studies found that endovascular therapy was more suitable for patients with drug-refractory, non-perforating arterial cerebral infarction, and avoiding intervention in the acute phase (≥3 weeks) of ischaemic stroke may reduce perioperative complications.7 The results of the follow-up WingSpan Stent System Post Market Surveillance...
(WAVE) trial further showed that the use of stents for ICAD under the Food and Drug Administration (FDA) approved indications has a low perioperative stroke and mortality (2.6%).9 The Wingspan One-Year Vascular Events and Neurologic Outcomes (WOVEN) trail, which analysed angiography, clinical events and neurological outcomes at 1 year after Wingspan stenting, showed that combined 1-year stroke and mortality (8.5%) were lower than those in the active medical therapy arm alone (12.2%) in the SAMMPRIS trial.10 In addition, the results of the multicentre, randomised controlled clinical trial CASSISS showed that for patients with symptomatic, severe intracranial artery stenosis, stent plus medical therapy was equivalent to medical therapy alone in preventing stroke or death.9 Considering the slightly different design of the above-mentioned studies and the inconsistency of the conclusions, it is necessary to pool the original data and conduct a more detailed analysis of the comparison between stenting and simple medical therapy alone in patients with symptomatic intracranial artery stenosis by a systematic review and IPD meta-analysis.11-14

Therefore, we established the 6S (SAMMPRIS and CASSISS) collaboration with the purpose of determining the safety and efficacy of stenting versus medical therapy alone in patients with symptomatic intracranial artery stenosis by a systematic review and IPD meta-analysis of randomised controlled trials (RCTs).

METHODS
Protocol registration and standard reporting
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols checklist for the protocol is available as supporting information (online supplemental additional file 1).15 This study was prospectively registered on PROSPERO (CRD42022369922) and will adhere to the PRISMA-IPD guidance for reporting the results of this systematic review and meta-analysis of IPD.16 Any modifications made to this protocol when conducting the study will be updated on PROSPERO.

Types of participants
Patients considered for study inclusion were 18–85 years of age and had a TIA or nondisabling ischaemic stroke, attributed to angiographically verified stenosis of 70%–99% of the diameter of a major intracranial artery. The stenosis is located at one of the major intracranial arteries (internal carotid artery, middle cerebral artery, intracranial vertebral artery or basilar artery). Key exclusion criteria included modified Rankin Scale (mRS) greater than 3, unstable neurological status (rapid worsening of the National Institute of Health Stroke Scale (NIHSS) score increasing ≥4 points within 48 hours prior to randomisation), and any haemorrhagic infarct within 14 days before enrolment. Detailed eligibility criteria are provided in table 1.

Types of interventions
The experimental intervention is endovascular therapy in addition to medical treatment. The following options of endovascular therapy are acceptable: balloon-mounted stent, and angioplasty followed by placement of a self-expanding stent. The comparator is medical therapy including antiplatelet therapy and appropriate management of patients’ individual stroke risk factors, mainly including hypertension, hyperlipidaemia and diabetes.

Types of outcome measures
Primary outcomes
- A composite of stroke or death within 30 days, or stroke in territory of qualifying artery beyond 30 days after randomisation.

Secondary outcomes
- Stroke or death within 30 days after randomisation.
- Stroke in territory of qualifying artery after randomisation.
- All-cause mortality.
- Any procedure-related adverse events.
- Any stroke recurrence in long-term including ischaemic, haemorrhagic, disabling or fatal stroke.
- Restenosis (≥50%) rate.
- Functional evaluation, including NIHSS score and mRS score.

Types of studies
To limit potential bias, we will only include RCTs. Observational studies will be excluded.

Identification of eligible studies
A systematic database search of PubMed, MEDLINE, EMBASE, the Cochrane Library and ClinicalTrials.gov. will be conducted to identify all relevant RCTs (figure 1). No limitation of language will be used, and publication date and study type filters corresponding to eligible criteria will be used. The following keywords will be used during the database searching: intracranial artery stenosis, angioplasty and stenting. The detailed search strategy can be found in online supplemental additional file 2. Additionally, to ensure a more comprehensive search, we will supplement the electronic search by scanning retrieved original articles and reference lists of previously published review articles. In addition, we will contact authors of included studies, research groups and prominent clinicians in the field to identify other published or unpublished RCTs that may be eligible for review.

Literature search results will be exported to Endnote along with titles and abstracts, where duplicate content will be removed and eligibility for inclusion can be assessed. We will attempt to identify duplicate publications of reported data from the same study by comparing author names, study locations and sample sizes. Eventually, we will contact the corresponding author to clarify possible overlaps or inconsistencies between multiple reports of the same study.

Two reviewers will independently screen the titles, abstracts and full-text articles of records retrieved through searches to assess whether studies meet the inclusion criteria. They will also identify and document the reasons...
why ineligible studies were excluded. Any disagreements between the examiners will be resolved through discussion, and a third investigator will be consulted if there are discrepancies at any stage of the process.

Data collection
For studies meeting our inclusion criteria, the review authors will send data requests for IPD analyses to the first or corresponding authors or both of all included trials, or to the trial sponsors when appropriate. If there is no response, we will send two follow-up emails at 2-week intervals. Study data will be noted as unavailable if no authors respond, or if all authors indicate that the data is unavailable or they cannot share it due to access restrictions. We will send up to four reminders before we exclude the study as unavailable. We will securely transfer all acquired IPDs according to data transfer guidelines. All randomised participants will be included in the pooled database and included in the intention-to-treat (ITT) analysis. The requested variables are as follows:

1. Study characteristics: title, authors, contact address, funding source, language, publication status, year of publication, place(s) and year(s) of study conduction, study design (eg, date of randomisation, eligibility criteria, follow-up period), trial methods (eg, method of

<table>
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<th>Table 1</th>
<th>Eligibility criteria for considering studies for the review</th>
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<td><strong>Inclusion criteria</strong></td>
<td><strong>Exclusion criteria</strong></td>
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<tr>
<td><strong>Patient</strong></td>
<td><strong>1. 18–85 years of age.</strong>&lt;br&gt;2. TIA or nondisabling stroke attributed to angiographically verified stenosis of 70%–99% of the diameter of a major intracranial artery (internal carotid artery, middle cerebral artery, intracranial vertebral artery or basilar artery).**</td>
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<td><strong>Intervention</strong></td>
<td><strong>Stenting with or without angioplasty.</strong></td>
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<td><strong>Comparison</strong></td>
<td><strong>Medical therapy alone including anti-platelet drugs and control of stroke risk factors.</strong></td>
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<td><strong>Outcomes</strong></td>
<td><strong>At least one of the following outcomes reported:</strong>&lt;br&gt;<strong>Primary outcomes</strong>&lt;br&gt;► A composite of stroke or death within 30 days, or stroke in territory of qualifying artery beyond 30 days after randomisation.&lt;br&gt;<strong>Secondary outcomes</strong>&lt;br&gt;► Stroke or death within 30 days after randomisation.&lt;br&gt;► Stroke in territory of qualifying artery after randomisation.&lt;br&gt;► All-cause mortality;&lt;br&gt;► Any procedure-related adverse events;&lt;br&gt;► Any stroke recurrence in long-term including ischaemic, haemorrhagic, disabling or fatal stroke.&lt;br&gt;► Restenosis (≥50%) rate;&lt;br&gt;► Functional evaluation, including NIHSS score and mRS score;**</td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td><strong>RCT</strong></td>
</tr>
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RCTs, randomised controlled trials; TIA, transient ischaemic attack.
Dealing with missing data

Data may be missing for some participants in one or more trials, or data may be missing for all participants in one or more trials (ie, variables were not measured and outcomes are missing). All missing data will be assessed according to the amount and type of loss (ie, missing completely at random, missing at random, missing not at random). If data were found to be missing at random or entirely at random, multiple imputation was used to impute missing covariates where computationally feasible. We will investigate the potential impact of imputation on the meta-analysis by performing a sensitivity analysis.

Assessment of risk of bias in included studies

Two reviewers will independently assess all included studies using the Cochrane Risk of Bias Assessment tool, focusing on sequence generation, allocation concealment, blinding (participants, personnel and outcome assessors), incomplete data, selective outcome reporting and assessment of other Bias.17 Each question assesses risk of bias in an objective manner in order to minimise disagreement among raters associated with more subjective areas of the risk of bias tool. Disagreement among authors will be resolved through discussion, and if consensus is not reached, a third reviewer will be sought. A statistician will be consulted for judgments related to the statistical analyses, if required.

Each item in the ‘risk of bias assessment’ will be assessed as having a low, high or unclear risk of bias, and we will provide the reasons for our judgement in the ‘risk of bias assessment’ table (online supplemental additional file 3). We will provide aggregated figures for the risk of bias assessment.

Data synthesis

Statistical analyses will be done with IPD on an ITT basis. Baseline characteristics between two treatment groups will be compared by use of the Cochran-Mantel-Haenszel test for categorical variables and analysis of variance for continuous variables stratified by trial. Treatment effects will be expressed as risk ratios and 95% CIs for binary outcomes, HRs and 95% CI for time-to-event outcomes, and mean difference and 95% CI for quantitative outcomes. Outcome events for 1 month, 1 year, 2 years, 3 years and the longest time point that can be followed up will be reported. We will first summarise the event rates with unadjusted Kaplan-Meier estimates at the longest available follow-up then conduct a series of random-effects meta-analyses of IPD. For the primary analysis, we will use a one-stage meta-analysis model for which we balance of baseline characteristics between treatment groups will also be examined to assess completeness of randomisation. We will reformat the data when necessary. We will also log all changes to check the validity and plausibility of the data and discuss any inconsistencies with the data provider. We will seek missing information about the study from the lead study author if required.
will synthesise IPD from all trials simultaneously while preserving the random allocations in the original trials by use of a Cox proportional hazard regression model with trial as a random effect. We will also test for interaction between the stenosis site and treatment group.

We will assess between-trial heterogeneity using the I² statistic, p values from the χ² test and between-study heterogeneity τ². Heterogeneity will be considered substantial when p<0.1. To quantify heterogeneity, I² statistic ranges are used to guide interpretation: 0%–40%: likely not important; 30%–60%: likely to represent moderate heterogeneity; 50%–90%: likely to represent considerable heterogeneity; 75%–100%: considerable heterogeneity. If we found substantial heterogeneity (I² greater than 50% according to the Cochrane systematic reviews of intervention handbook), we will explore potential causes of heterogeneity by performing subgroup analyses and meta-regression. We will use random-effects meta-analyses as appropriate. We will consider any statistical heterogeneity when interpreting the results.

**Subgroup analysis**

We plan to perform subgroup analyses of the primary and secondary outcomes between treatment groups based on baseline characteristics: stenosis site, stenosis degree, qualifying event, qualifying artery, timing of stenting, race, age and other characteristics. We determined whether there were differences of effect size among subgroups based on the p values from tests for subgroup differences.

**Sensitivity analysis**

We will perform sensitivity analyses to assess the validity and robustness of the results to the primary outcome. We will limit our analysis to the following:

- When multiple studies did not provide the IPD, we will combine their pooled data with the IPD to assess the robustness of including or excluding these studies.
- Studies of varying quality, as will be assessed by performing the analysis excluding studies at high risk of bias.
- Large studies, to determine the extent to which they dominate the results.
- One-stage fixed-effect analysis with a Cox regression model stratified by trial; If there is disagreement between the two models, we present both results; otherwise, we present only the results for the random-effects model.
- In the two-step method, we will first analyse separately each trial using IPD, before combining them using a random-effects meta-analysis model to account for variability between trials.

**Statistical software**

We will use Stata, V.16.1, and R, V.4.1.1 for analysis.

**Ethics and dissemination**

Ethical approval and individual patient consent will not be required in most cases since this IPD meta-analysis will use pseudonymised data from randomised controlled trials. Results will be disseminated through peer-reviewed journals and international conferences.

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**Contributors**

TW was involved in study conception and design, protocol development, study oversight, and manuscript drafting and editing. ZK and HG were involved in manuscript drafting and editing. CPD, OZ and EA contributed to data collection and interpretation. JL, PG and HW supervised the study protocol and provide guidance in study design and manuscript editing. LJ provided funding and correspondence to this article.

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**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Supplemental material**

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