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Blood pressure management in reperfused ischemic stroke (Protocol)

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[Intervention Protocol]

Blood pressure management in reperfused ischemic stroke

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of intensive systolic blood pressure management (target less than 160 mmHg) versus conventional management (target less than 180 mmHg) in people undergoing ischemic stroke reperfusion via systemic thrombolysis or endovascular thrombectomy.

BACKGROUND

Description of the condition

An ischemic stroke (80% to 85% of all strokes) is caused by the disruption of blood flow, leading to brain tissue damage and functional loss, with subsequent impact on individuals' life and functionality [1]. According to the Global Burden of Disease Study conducted in 2021 [2, 3], stroke is the third leading cause of combined death and disability (measured in disability-adjusted life years) and the second leading cause of death worldwide [2, 3]. With the aging of the population, strokes have become a significant contributor to the personal and financial burdens on society [4]. The direct and indirect cost of strokes in the US was estimated at 52.8 billion US dollars annually from 2017 to 2018 [5]. Ischemic stroke is usually caused by the thrombotic occlusion of a cerebral artery, with therapeutic alternatives in the acute period including intravenous thrombolytic treatment with recombinant tissue plasminogen activator, intra-arterial fibrinolysis, and endovascular thrombectomy [4, 6]. Thrombolytic drugs aim to dissolve the thrombus, thereby restoring blood flow. Endovascular thrombectomy involves recanalization therapies in which the blood clot is removed using a mechanical device. The ultimate goal is to eliminate the clot, achieving recanalization of the affected cerebral tissue. If the procedure is performed in a timely and uncomplicated manner, the neurologic functional outcome can improve significantly [1, 7]. Despite recanalization efforts, 50% to 60% of people undergoing endovascular therapy for a stroke died or remained disabled at 90 days regardless of whether it was a primary or extended window intervention [8].

Description of the intervention and how it might work

The leading challenge in acute ischemic stroke research is currently beyond reperfusion and focuses on ischemia-reperfusion injuries, encompassing blood–brain barrier disruption, cerebral edema, and intraparenchymal hemorrhage [9]. Arterial hypertension stands as one of the most significant modifiable risk factors for stroke onset [10]. Nonetheless, the relationship between blood pressure at the time of stroke onset and the outcomes is complex. The impact of blood pressure on the outcomes of these people is influenced by multiple factors, including baseline blood pressure, degree of collateral circulation, size of the ischemic penumbra area, and achieved recanalization, among others [10]. Managing blood pressure during and after a cerebral revascularization procedure is crucial. Sustained high blood pressure during and after thrombectomy or thrombolysis (or both) can worsen clinical outcomes due to bleeding and cerebral edema as a result of increased susceptibility of ischemic tissue to pressure variations, leading to microvascular integrity loss. However, treatment to reduce blood pressure may decrease perfusion pressure and consequently increase the size of the ischemic lesion [10, 11]. Given all this complexity, the optimal blood pressure management in people with reperfused ischemic stroke is uncertain [10].

People undergoing cerebral reperfusion typically receive postreperfusion care in stroke units or intensive care units equipped with continuous blood pressure monitoring using invasive or non-invasive devices [12, 13, 14]. Current guidelines recommend maintaining blood pressure below 180/105 mmHg for 24 hours after endovascular thrombectomy or systemic thrombolysis (or both) [13, 14], with no specific blood pressure-lowering agent recommended [14]. Options for managing arterial hypertension include labetalol, nicardipine, and clevidipine [13]. However, data gathered from the StrokeNet survey showed that most US institutions use a systolic blood pressure target lower than 140 mmHg in reperfused patients [15]. Observational studies reported that lower systolic blood pressure after successful endovascular thrombectomy and systemic thrombolysis may be associated with better functional outcomes [8]. Non-randomized studies suggested an association between increased systolic blood pressure values and symptomatic intraparenchymal hemorrhage, as well as mortality, in the setting of successful reperfusion after therapy [15, 16]. Specifically, one prospective multisite observational study identified a maximal systolic blood pressure of 160 mmHg within 24 hours after endovascular thrombectomy distinguished between people with good versus poor functional outcomes [17]. Others showed that moderate systolic blood pressure levels between 140 mmHg and 160 mmHg were associated with better patient outcomes [16]. Nevertheless, one randomized trial conducted on Chinese people who underwent successful endovascular thrombectomy discovered that maintaining systolic blood pressure below 120 mmHg was harmful with worse functional outcomes [18]. In recent years, several trials have been conducted to help clarify this area of uncertainty [8, 9, 12, 17, 18, 19].

Why it is important to do this review

Current recommendations in the guidelines for ischemic stroke management suggest maintaining blood pressure below 180/105 mmHg for 24 hours after endovascular thrombectomy [13, 14]. Similar blood pressure values are recommended in cases of systemic thrombolysis. However, the evidence supporting these recommendations stems from non-randomized studies with low-certainty evidence [13, 14]. Some studies have suggested that achieving lower values of systolic blood pressure (reducing to less than 160 mmHg) after the procedure would be beneficial in achieving the best functional outcome and reducing the risk of symptomatic intracranial hemorrhage [10, 17].

Considering the global incidence of ischemic strokes, the investments made in procedures for achieving cerebral reperfusion, the recognized efficacy of reperfusion as a treatment for ischemic stroke, and the crucial significance of blood pressure management during the acute phase, along with the existing uncertainties in current recommendations and recent clinical trials aiming to provide clarity, it becomes essential to establish the appropriate blood pressure management for this population. This is crucial to minimize the risk of hemorrhage and complications, confine the ischemic area, and thereby optimize the functional outcome, resulting in an improved quality of life for individuals and a reduced burden on individuals, families, healthcare systems, and society as a whole.

OBJECTIVES

To assess the benefits and harms of intensive systolic blood pressure management (target less than 160 mmHg) versus conventional management (target less than 180 mmHg) in people undergoing ischemic stroke reperfusion via systemic thrombolysis or endovascular thrombectomy.

METHODS

We will follow the Methodological Expectations for Cochrane Intervention Reviews when conducting the review [20], and PRISMA 2000 [21] for the reporting.

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) and cluster-RCTs. Following the guidelines in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* [22], we will exclude cross-over trials, because they may have a potential withdrawal, rebound, or carry-over effect during or after the wash-out period. We will exclude quasi-RCTs (controlled trials that used inappropriate strategies of allocating interventions) and non-randomized clinical trials, following the algorithm outlined in Chapter 24 of the *Cochrane Handbook* due to the availability of RCTs that address our research questions [23].

Types of participants

We will include adults (aged older than 18 years) with acute ischemic stroke (computed tomography or magnetic resonance scanning having excluded intracranial hemorrhage before randomization) reperfused by systemic thrombolysis or endovascular thrombectomy. Systemic thrombolysis could be performed with different drugs, doses, and administration routes (intravenous or intra-arterial) established by the studies, while endovascular thrombectomy could involve thromboaspiration, stent retriever thrombectomy, aspiration, or a combination of techniques. We will include any postprocedure reperfusion status defined by the authors as inclusion criteria for the study.

If we identify studies in which only a subset of participants is relevant to this review, we will include these studies if data are available separately for the relevant subset, or if more than 80% of participants meet the inclusion criteria.

Types of interventions

We will include studies comparing intensive systolic blood pressure management (target any systolic blood pressure objective less than 160 mmHg) versus conventional management (target systolic blood pressure less than 180 mmHg) in people who underwent systemic thrombolysis or endovascular thrombectomy for reperfusion of ischemic stroke.

If studies use different systolic blood pressure management cutoff points, we will use the classification defined by the study authors.

We will include co-interventions, provided they are not part of the randomized treatment, and are comparable in both the intervention and comparator groups, to establish a fair comparison. If a study includes multiple arms, we will include any arm that meets the inclusion criteria for this review.

Interventions

Intensive systolic blood pressure management (target any systolic blood pressure objective less than 160 mmHg) for at least 24 hours after the therapeutic procedure (systemic thrombolysis or endovascular thrombectomy), monitored through invasive or non-invasive methods and utilizing the recommended intravenous antihypertensive medications as defined by study authors (usually nicardipine, although the use of other antihypertensive agents such as labetalol, hydralazine, etc. could be allowed). According to the recommendations from the European and American guidelines, the minimum duration of the intervention will be 24 hours postprocedure [13, 14], with randomization and blood pressure management initiated within the first hour after the procedure or according to the study authors' specifications.

The systolic blood pressure cutoff of less than 160 mmHg was chosen as it is below current guideline recommendations, with the aim of including the greatest number of RCTs comparing targets below the current guideline thresholds [13, 14].

Comparators

Conventional systolic blood pressure management (target systolic blood pressure less than 180 mmHg) for at least 24 hours after the therapeutic procedure (systemic thrombolysis or endovascular thrombectomy), monitored through invasive or non-invasive methods and utilizing the recommended intravenous antihypertensive medications as defined by study authors (usually nicardipine, although the use of other antihypertensive agents such as labetalol, hydralazine, etc. could be allowed). According to the recommendations from the European and American guidelines, the minimum duration of the intervention will be 24 hours postprocedure [13, 14], with randomization and blood pressure management initiated within the first hour after the procedure or according to the study authors' specifications.

Outcome measures

We will not exclude a study if it fails to report more than one of our critical or important outcome measures of interest. We will only exclude studies if none of our outcomes of interest was measured and provided there is evidence to support this (e.g. contact with study authors, access to the original protocol, etc.).

Critical outcomes

- **Clinical function:** assessed at the end of the scheduled follow-up period, measured on the modified Rankin Scale (mRS) (a standard global 7-level measure of disability; score 0 to 2 indicating favorable functional outcome, score 3 to 6 indicating poor outcome, dependence, or death). Given that some studies use a definition of 'favorable outcome' as a score of 0 to 1, we also will look for data on the number of participants in each individual mRS category. If the mRS score is not reported, we will use the study's definition of functional outcome. There is no established minimal clinically important difference (MCID), so we will consider a change in risk ratio (RR) of 25% as the MCID for the dichotomous outcome. For the continuous outcomes (e.g. each individual mRS category), we will consider an MCID of 0.5 standard deviations [24].
- **Health-related quality of life:** assessed on a three-level EuroQoL 5-Dimension Self-Report Questionnaire (EQ-5D) or any other validated tool as defined by the study authors. The data will be analyzed as continuous data, with the primary measure being the total score at follow-up. MCID will range from 0.08 to 0.12 for EQ-5D [25]. We plan to calculate standardized mean differences with 95% confidence intervals if data are pooled from studies using different instruments to measure quality of life.

- **Neurologic adverse events:** assessed as the frequency of postprocedural intracerebral hemorrhage (including symptomatic intracranial hemorrhage or intracranial hemorrhage (or both) of any type in brain imaging within seven days of treatment or less) or malignant cerebral edema. We defined symptomatic intracranial hemorrhage according to the criteria used in the third European Cooperative Acute Stroke Study (ECASS III) [26]. When symptomatic intracranial hemorrhages are not reported according to these criteria, we will use the study's definition. Note that symptomatic intracranial hemorrhage includes hemorrhagic transformation of the infarct, hemorrhage elsewhere in the brain remote from the infarct, and hemorrhage into the spaces surrounding the brain. Malignant cerebral edema refers to a condition characterized by rapid neurologic deterioration accompanied by substantial brain swelling seen on computer tomography or magnetic resonance imaging, which often leads to death or poor functional outcomes.

Important outcomes

- **Neurologic status:** assessed by NIHSS (National Institutes of Health Stroke Scale) scores at the end of follow-up. We will define a favorable neurologic outcome as an NIHSS score of 0 to 1. As no MCID is established, we will consider a change in RR of 25% for dichotomous variables (e.g. good outcome). For continuous outcomes (e.g. each individual NIHSS score), we will consider an MCID of 0.5 standard deviations.
- **All-cause mortality:** assessed by the frequency of death from all causes following a stroke during the acute phase (within seven to 14 days) and at the end of scheduled follow-up (the established minimum clinical follow-up will be 90 days).
- **Hospital length of stay:** assessed by median duration of hospitalization in days. As no MCID is established, we will consider an MCID of 0.5 standard deviations.
- **Other adverse events:** assessed by the frequency of other adverse events reported in the studies, such as heart failure, arterial hypotension, sepsis, arterial re-occlusion, aspirational pneumonia, pseudoaneurysm at the puncture site, non-cerebral hemorrhage, and other reported adverse events occurring at any point during the established follow-up.

Timing of outcome measurement

We will categorize outcomes into two sets of time points.

- Short-term postintervention (defined as zero to two weeks postintervention) to detect illness recovery/symptom reduction following the intervention and any adverse events [27].
- Long-term (defined as longer than two weeks postintervention) as a measure of medium to long term to detect illness recovery/symptom reduction [27].

When multiple results are reported for each outcome, we will include the longest follow-up period in each category.

Search methods for identification of studies

Electronic searches

We will search the following sources from the inception of each database to the date of search and will place no restrictions on the language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (latest issue)
- MEDLINE (Ovid MEDLINE ALL 1946 to date of search)
- Embase (Ovid; 1974 to date of search)
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch/)

The details of the search strategies can be found in Supplementary material 1.

Searching other resources

Based on the results of the database searches, we will conduct a grey literature search using Google Scholar. We will also consider additional citation-based search methods based on selected articles, such as forward citation searches using Scopus and Google Scholar, and searches for related articles through MEDLINE via PubMed.

We will evaluate the inclusion of the Global Index Medicus after obtaining the results, in order to retrieve studies from low- and middle-income countries.

In addition, in an attempt to identify further published, unpublished, ongoing, or planned trials, we will examine the reference lists of relevant trials and contact professional organizations in stroke, neurology, neuroradiology, and interventional radiology, and authors and researchers active in the field.

We will handsearch the following conference proceedings and stroke and neurologic journals: *Stroke*, *Cerebrovascular Diseases*, *International Journal of Stroke*, *Journal of Stroke and Cerebrovascular Diseases*, *Neurology and Journal of Neurology*, *Neurosurgery*, and *Psychiatry*. We will check multiple international conference proceedings on stroke and specifically on thrombolysis and thrombectomy. These include all European Stroke Conferences (since 1992, annual since 1994), all International Stroke Conferences hosted by the American Heart Association (annual), all World Stroke Conferences (annual), and all Thrombolysis in Acute Ischaemic Stroke symposia (biannual).

As we approach the review's publication date, we will update our searches of MEDLINE (Ovid) and Embase (Ovid) to identify any withdrawals, errors, or corrections in the included studies. We will also search RetractionWatch (retractionwatch.com).

Data collection and analysis

Selection of studies

We will use Covidence software for study selection [28]. Two review authors (LBV and SD) will independently screen the titles and abstracts of references identified by the searches. Any disagreements between the authors will be resolved with input from a third review author (LIG). We will obtain full-text copies of all potentially relevant reports. The same two review authors (LBV and SD) will independently screen the full-text studies and record reasons for the exclusion of excluded studies. Any disagreements between the authors will be resolved with input from a third review author (LIG) if needed. If we cannot resolve a disagreement, we will categorize the study as awaiting classification and will contact

the study authors for clarification. We will present a PRISMA flow diagram to show the process of study selection [21]. We will list all articles excluded after full-text assessment in the characteristics of excluded studies table and will provide the reasons for exclusion [21].

Data extraction and management

For studies that fulfill our inclusion criteria, two review authors (LBV and SD) will independently extract key information, using a piloted data extraction form, on participants, interventions, and comparators. The review authors will not be blinded to journals or institutions. Any disagreements between the authors will be resolved by discussion, with input from a third review author (LIG) if needed.

One review author (LBV) will enter the data into Review Manager [29]. Another two review authors (LIG and SD) will check and transfer study data into the analyses.

We will extract the following data from the reports.

- Methods
  - Study design: study dates (start date to end date; if dates are not available, we will report this) and study settings and country, language of publication, and study identifier
- Participants
  - Inclusion and exclusion criteria
  - Participant details, baseline demographics (mean age, age range, gender, residential location, diagnosis criteria used for acute ischemic stroke, severity of the condition, location of the arterial occlusion, time interval from stroke onset to randomization, treatment performed to achieve reperfusion in stroke, time to actual delivery of therapy/recanalization, modality of percutaneous vascular intervention or agent and dose of pharmacologic thrombolytic therapy used, early ischemic changes on computer tomography according to the Alberta Stroke Program Early CT Score (ASPECTS), inclusion criteria and exclusion criteria)
  - Numbers of participants in each treatment group with outcome events
- Interventions and comparisons, according to the Template for Intervention Description and Replication (TIDieR) checklist [30, 31]
  - Name of the intervention
  - Why: rationale, theory, or goal of the elements essential to the intervention
  - What: physical or informational materials used in the intervention, procedures, activities, or processes used in the intervention
  - Who provided: expertise, background and specific training given
  - How: describe modes of delivery
  - Where: describe the location where the intervention occurred, including infrastructure and features
  - When/how much: the number of times the intervention was delivered over a period of time
  - Tailoring: describe if personalization or adaptations were planned
  - Modifications: during the course of the study
  - How well: measurements of adherence or fidelity
- Outcomes
  - Definitions of relevant outcomes, method and timing of outcome measurement, as well as any relevant subgroups to the review
- Study funding sources
- Declarations of interest, by primary investigators

We will report these data in the characteristics of included studies table and summarize them in the results section. We will contact the authors of the included studies to inquire whether they are willing to answer questions regarding their studies. We will document these communications. We will seek relevant missing information on the study from the primary study authors if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we will maximize the information yield by collating all available data, and we will use the most complete data set, aggregated across all known publications. We will list duplicate publications, companion documents, multiple reports of a primary study, and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included study. We will also list duplicate publications, companion documents, multiple reports of a study, and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of the excluded study.

Data from clinical trial registers

If data from included studies are available as study results in clinical trial registers, such as ClinicalTrials.gov or similar sources, we will make full use of this information and extract the data. If there is also a full publication of the study, we will collate and critically appraise all available data. If the published and unpublished data do not match, we will ask the study authors for clarification. If we receive no response, we will present the discrepancies in the review. If an included study is labeled as completed in a clinical trial register but no additional information (study results, publication, or both) is available, we will add this study to the characteristics of studies awaiting classification table.

Risk of bias assessment in included studies

Two review authors (LBV and SD) will independently assess the risk of bias for the results of the main outcomes using the Cochrane RoB 2 tool for all outcomes at the latest follow-up [32, 33]. For all outcomes, we will analyze data using the intention-to-treat principle [34]. We will resolve disagreements by consulting a third review author (LIG). If adequate information is unavailable from the publications, trial protocols, clinical study reports, or other sources, we will contact the study authors for more details on the risk of bias items.

We will assess the risk of bias for all RoB 2 domains and judge each domain as 'high risk of bias,' 'some concerns,' or 'low risk of bias' using the responses to the signaling questions and algorithms within the RoB 2 tool. Domains include bias caused by the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. The tool algorithm will be used to reach an overall risk of bias for each outcome. We will quote evidence to support our judgments in the risk of bias table and, if we disagree

with a judgment recommended by the algorithm, we will include an explicit statement as to why. We will manage our risk of bias assessments using the RoB 2 Excel tool [33]. All data will be publicly available, as supplementary material, in a public repository.

For cluster-RCTs, we will use the RoB 2 tool and an additional domain specifically for cluster-RCTs from the archived version of the tool (domain 1b – "bias arising from the timing of identification and recruitment of participants"), available at www.riskofbias.info, with its corresponding signaling questions. We will follow the guidance in the *Cochrane Handbook* (Section 23.1.2 and Table 23.1.a) [22].

Measures of treatment effect

We will express dichotomous data (e.g. clinical functional outcome as a favorable functional outcome and poor functional outcome) as an RR with 95% confidence intervals (CIs). For continuous outcomes (e.g. neurologic status assessed by NIHSS scores measured on the same scale), we will estimate the intervention effect using the mean difference (MD) with 95% CIs. When data are pooled from studies that used different instruments to measure the same outcome, we plan to calculate SMDs with 95% CIs. We will enter data presented as a scale with a consistent direction of effect, and multiply the SMD by a standard deviation that is representative of the pooled studies (e.g. the standard deviation from a well-known scale used by several of the studies included in the analysis on which the result was based). We will undertake meta-analyses only when it is meaningful (i.e. when treatments, participants, and the underlying clinical questions are similar enough for pooling to make sense). We will describe skewed data reported as medians and interquartile ranges narratively.

Unit of analysis issues

We will take into account the level at which randomization occurred, and multiple observations for the same outcome. If more than one comparison from the same study is eligible for inclusion in the same meta-analysis, we will either combine groups to create a single pair-wise comparison, or appropriately reduce the sample size so that the same participants do not contribute data to the meta-analysis more than once (splitting the shared group into two or more groups). Although the latter approach offers some solutions for adjusting the precision of the comparison, it does not account for correlation arising from the inclusion of the same set of participants in multiple comparisons [34]. The unit of analysis will be the participants with reperfused acute ischemic stroke by thrombolysis or thrombectomy.

For cluster-RCTs, we will consider the cluster as the unit of analysis, not the individual participants, in order to avoid unit of analysis errors, as stated in Section 23.1.1 of the *Cochrane Handbook* [22]. If the effect measure for the cluster is not determined by appropriate methods in the included studies, we will multiply the standard error of the effect estimate (from an analysis ignoring clustering) by the square root of the design effect, calculated using an intracluster (or intraclass) correlation coefficient (ICC) of 0.02, following guidance in Sections 23.1.4 and 23.1.5 of the *Cochrane Handbook* [22].

Dealing with missing data

If possible, we will obtain missing data from the authors of the included studies. We will carefully evaluate important numerical data, such as screening; randomly assigned participants; and intention-to-treat, as-treated, and per-protocol populations in our risk of bias assessments. For this, we will investigate attrition rates (e.g. dropouts, losses to follow-up, and withdrawals), and critically appraise issues concerning missing data and the use of imputation methods (e.g. last observation carried forward). We will analyze available data only. When this is not possible, and when missing data are deemed to introduce significant bias, we will explore the impact of including such studies in the overall assessment of results through a sensitivity analysis.

Reporting bias assessment

We will undertake extensive literature searching without restrictions on publication date or language in order to limit reporting bias. We will use study protocols and trial registrations to assess studies for selective reporting. If we include 10 studies or more per outcome, we will use funnel plots to assess small-study effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to study size, poor methodologic design (and hence bias of small studies), and selective non-reporting [35]. Therefore, we will interpret the results carefully [36]. We will not perform statistical analysis for funnel plots asymmetry as these tests typically have low power, following guidance in Chapter 13 of the *Cochrane Handbook* [37].

Synthesis methods

We will complete all syntheses using Review Manager [29]. We plan to undertake a meta-analysis only if we judge the participants, interventions, comparisons, and outcomes are sufficiently similar to ensure a result that is clinically meaningful. In the primary analysis, we will include all studies regardless of their risk of bias.

We will primarily summarize data using a random-effects model [38]. We will interpret random-effects meta-analyses with consideration for the whole distribution of effects, and present CIs. We will perform statistical analyses according to the statistical guidelines presented in Chapter 10 of the *Cochrane Handbook* [39].

If meta-analysis is not possible, we will summarize the results using a narrative synthesis, according to Synthesis Without Meta-analysis guidelines, instead of a pooled statistical synthesis. We will follow Chapter 12 of the *Cochrane Handbook* [40].

We will perform subgroup analyses using the methodology described by Deeks and colleagues, as recommended in Section 10.11.3 of the *Cochrane Handbook* [39].

Investigation of heterogeneity and subgroup analysis

We will visually examine the variability in point estimates and the overlap in CIs. We will use the I^2 statistic to estimate the degree of heterogeneity present among the trials in each analysis [41]. If we identify substantial unexplained heterogeneity, we will report it, and explore possible causes by prespecified subgroup analysis. We will use the following approximate guide to interpretation, outlined in Chapter 10 of the *Cochrane Handbook* [39].

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

We will avoid the use of absolute cutoff values, but interpret the I^2 statistic in relation to the size and direction of effects, and the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or CI for the I^2 statistic).

We expect the following characteristics to introduce clinical heterogeneity, and we plan to conduct subgroup analyses for these, including an investigation of interactions [42].

- Subgroups of intervention based on target systolic blood pressure levels: below 160 mmHg, below 140 mmHg, and below 120 mmHg
- Gender/sex: men versus women, considering trials conducted on one gender exclusively or with over 80% of participants representing a specific gender to establish the subgroups
- Socioeconomic status based on country income level: low-, middle- and high-income countries, based on the World Bank classification (available at the World Bank website)
- Stroke severity: according to the NIHSS score (less than 17 points versus 17 points or greater, range 0 to 42 points, with higher scores indicating greater severity), or using each trial's cutoff for severe stroke
- Procedure performed: systemic thrombolysis or endovascular thrombectomy, or both (type)

We will use the formal test for subgroup interactions in Review Manager [29], acknowledging its limitations due to its observational nature and low power to detect differences with fewer than 10 studies per category [34].

Equity-related assessment

We will explore health inequity through two characteristics defined by PROGRESS-Plus: gender/sex and socioeconomic status [43]. See Supplementary material 2 for additional details about study characteristics with equity-related implications.

The prevalence of stroke and its complications is higher in females, attributed to multiple factors including biologic, clinical, social, and healthcare system-related factors [2, 3, 5]. Consequently, we intend to conduct a subgroup analysis to assess whether the reviews consider the incorporation of different sexes.

Additionally, we will analyze the impact of residential location, as in 2019, the World Bank reported that low-income countries exhibited an age-standardized stroke-related mortality rate of 3.6 (95% uncertainty interval 3.5 to 3.8) times higher and an age-standardized stroke-related DALY rate of 3.7 (95% uncertainty interval 3.5 to 3.9) times higher than those of high-income countries. Considering this reason for inequity, we will add socioeconomic status based on residential location as a subgroup analysis.

In our subgroup analysis, we will aim to conduct an equity-related assessment that considers the context in which the interventions and studies included were conducted. This approach will allow us to explore the implications of our findings across diverse populations. For the subgroup analysis, we will extract sex and residential location disaggregated data. Where these data are not reported, we will contact the study authors to obtain them.

We will create a separate summary of findings table to describe the critical outcomes (clinical function, health-related quality of life, and neurologic adverse events) based on health inequity. Additionally, in the 'Equity-related implications for practice' and 'Equity-related implications for research' sections of the conclusions, we will address the applicability of the results to different populations analyzed in our subgroups, highlighting potential disparities and context-specific factors that may influence outcomes and practice applicability.

Sensitivity analysis

We plan to perform the following sensitivity analyses for the critical outcomes (clinical functional outcome, health-related quality of life, and neurologic adverse events) to explore the influence of the following factors on effect sizes, according to Section 10.14 of the *Cochrane Handbook* [39].

- Study design: excluding studies with cluster randomization
- Methodologic quality: removing studies with an overall high risk of bias
- Published data status: excluding unpublished data

Certainty of the evidence assessment

We will present the overall certainty of the evidence for each outcome specified below, according to the GRADE approach, which takes into account issues related to internal validity (overall risk of bias, inconsistency, imprecision, publication bias) and external validity (directness of results). Two review authors (LBV and SD) will independently rate the certainty of the evidence for each outcome. We will resolve any differences in assessment by discussion, or consulting a third review author (LIG).

We will present a summary of the evidence in a summary of findings table. This will provide key information about the best estimate of the magnitude of effect, in relative terms and absolute differences, for each relevant comparison of alternative management strategies; the numbers of participants and studies addressing each important outcome; and a rating of overall confidence in effect estimates for each outcome. We will create the summary of findings table using the methods described in the *Cochrane Handbook* [44], Review Manager, and GRADEpro GDT software [29, 45, 46].

We will justify all decisions to downgrade the certainty of the evidence using informative footnotes and GRADE guidelines [47].

We will create a summary of findings table that includes all outcomes listed in the Outcome measures section for the comparison of intensive systolic blood pressure management versus conventional systolic blood pressure management, focusing on the longest follow-up and prioritizing continuous outcomes.

Consumer involvement

We will not involve consumers in this review due to limited resources.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016085.

Supplementary material 1 Search strategies

Supplementary material 2 Summary of the characteristics of participants we should expect to see in the evidence and the actual participants' characteristics extracted from the included studies

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Dru Riddle, Cochrane TCU Affiliate/US Network
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Sara Hales-Brittain, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Addie-Ann Smyth, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Anne Lawson, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Craig Anderson at The George Institute for Global Health, Australia (clinical/content review); Lili Song, Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China (clinical/content review); Hisatomi Arima, Department of Preventive Medicine and Public Health, Fukuoka University (clinical/content review); FNU Simran (consumer review); Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review); Sarah Louise Klingenberg, Cochrane Hepato-Biliary Group (search review)

Contributions of authors

All review authors read and approved the final draft of the protocol.

LBV concepted the review and searched studies for the Background section.

LBV, SD, CE, MAB, DI, and LIG drafted the protocol.

LIG co-ordinated the review.

CE, LBV: developed the search strategy.

Declarations of interest

LBV: none. LBV was not involved in the editorial process.

SD: none.

CE: none.

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- No external sources of support received., Other

  No external sources of support received.

Registration and protocol

Cochrane approved the proposal for this review in November 2023.

Data, code and other materials

As part of the published Cochrane Review, the following will be made available for download for users of the Cochrane Library: full search strategies for each database; full citations of each unique report for all studies included, ongoing or awaiting classification, or excluded at the full-text screen, in the final review; study data, including study information, study arms, and study results or test data; consensus risk of bias assessments; and analysis data, including overall estimates and settings, subgroup estimates, and individual data rows. Appropriate permissions will be obtained for such use. Analyses and data management will be conducted using Cochrane's authoring tool, Review Manager Web, using built-in computation methods. Template data extraction forms from Covidence will be available from the authors upon reasonable request.

Data sharing not applicable to this article as it is a protocol, so no datasets were generated or analysed.

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