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Covert Ischemic Brain Infarction in Acute and Chronic Blood Pressure Elevation: Protocol for a Systematic Review

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ADMINISTRATIVE INFORMATION

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INTRODUCTION

Review question / Objective To synthesize and assess the certainty of evidence on the prevalence of covert brain infarction among adults with acute and chronic blood pressure elevation.

Our specific objectives are:

1) To estimate the prevalence of neuroimaging-defined acute ischemic lesions in adults presenting with acutely elevated blood pressure in the absence of focal neurological deficits.

2) To estimate the prevalence of neuroimaging-defined covert ischemic brain infarcts in adults with chronic hypertension.

3) To assess the risk of bias of included studies and the certainty of evidence using an adapted GRADE approach.

Rationale Covert brain infarctions are cerebral ischemic lesions that occur in the absence of clinically apparent neurological deficits such as motor weakness, sensory disturbances, or aphasia(1). They are commonly detected incidentally on neuroimaging. Unlike infarctions affecting eloquent brain regions that produce clear neurological symptoms, covert infarctions often involve brain areas where injury does not lead to immediately recognizable deficits or where functional compensation occurs(2). Despite their subclinical presentation, covert brain infarctions are clinically important because they are associated with an increased risk of subsequent symptomatic stroke, cognitive decline, dementia, and other major cardiovascular events, thereby contributing substantially to long-term morbidity(3,4). Epidemiological studies suggest that covert infarctions are present in up to one fifth of older adults and occur more frequently in individuals with vascular risk factors, particularly hypertension(4,5). Covert infarctions are also frequently detected on brain MRI performed for other indications, including after symptomatic ischemic stroke, where their presence has been associated with an increased risk of recurrent cerebrovascular events(6).

Interpretation of the available literature requires consideration of the imaging modality used for lesion detection. Most evidence regarding covert brain infarctions is derived from MRI-based studies because CT lacks sufficient sensitivity for the detection of many small ischemic lesions. This limitation is particularly important for acute covert infarctions, which often cannot be visualized on CT in the absence of overt neurological symptoms prompting dedicated stroke imaging. Although chronic infarcts may be detected on CT, small lacunar lesions can be difficult to distinguish from enlarged perivascular spaces and other chronic structural abnormalities. As a result, MRI remains the preferred imaging modality for the identification of covert brain infarctions and provides a more accurate assessment of their prevalence and distribution. Accordingly, current definitions and epidemiological studies of covert brain infarction are largely based on MRI findings rather than CT imaging(3,7).

Arterial hypertension is one of the most important modifiable risk factors for cerebrovascular disease and plays a central role in the development of cerebral small vessel disease and ischemic brain injury(8). Chronic hypertension contributes to structural alterations of small cerebral vessels, including endothelial dysfunction and lipohyalinosis, and impaired autoregulation, which may promote the development of covert ischemic lesions(8). In addition to chronic exposure, marked elevations in blood pressure are recognized triggers of acute cerebrovascular events. However, acute hypertension may also occur as a physiological response to cerebral ischemia, and the temporal relationship between elevated blood pressure and covert ischemic injury remains incompletely understood.

Observational imaging studies have suggested an association between elevated blood pressure and covert cerebrovascular lesions detected on brain imaging. In large community-based MRI cohorts, covert brain infarctions have been reported in approximately 10% of participants(9). However, the reported prevalence and the strength of associations with hypertension vary across populations and study designs. Current neurological guidelines do not recommend routine neuroimaging in asymptomatic individuals with severe or chronic hypertension. Consequently, covert cerebrovascular lesions may remain undetected in a large population at increased vascular risk. A comprehensive synthesis of the available evidence examining the relationship between both acute and chronic blood pressure exposure and covert brain infarction is therefore needed to better understand the burden and potential clinical implications of subclinical cerebrovascular injury.

The terms covert brain infarcts and silent brain infarcts are often used interchangeably in the literature to describe imaging evidence of cerebral infarction in the absence of clinically apparent stroke. In this review, we decided to use the term covert brain infarction, as neurological symptoms may be either absent, or too subtle to be attributed to a focal lesion(1). This review is restricted to ischemic lesions(10).

Condition being studied Given that the methodological focus of this review is on prevalence and incidence studies, eligibility criteria were structured using a CoCoPop (Condition–Context–Population) framework rather than PICO, which is not suited to descriptive epidemiological questions without an intervention or comparator(11).

This review focuses on MRI defined covert brain infarction in adults with acutely elevated blood pressure and in populations with chronic hypertension. Only studies using MRI-based lesion assessment will be included, as compared with CT, MRI provides substantially greater sensitivity for the detection of small and clinically covert ischemic lesions, thereby reducing the risk of outcome misclassification across studies.

Covert brain infarction will be defined as ischemic brain lesions presenting without focal symptoms corresponding to the affected lesion (1). We include both embolic and non-embolic infarcts due to small vessel disease, including lacunar infarcts and small subcortical infarcts. We explicitly exclude imaging findings that do not represent focal infarction, including white matter hyperintensities, enlarged perivascular spaces, cerebral microbleeds, cortical microinfarcts and generalized brain atrophy, as these reflect other aspects of cerebral small vessel disease rather than discrete infarction(12).

Studies without MRI-based ischemic outcomes will be excluded.

METHODS

Search strategy The systematic literature search strategy will be developed collaboratively by the study team, with methodological guidance from an information specialist (MvG), who will lead its implementation across the selected bibliographic databases. An initial search strategy is developed in Ovid MEDLINE using controlled vocabulary and free-text terms, covering the three main concepts "covert brain lesions", "hypertension" and "magnetic resonance imaging". The search

strategy is then translated to Embase (Ovid) and Web of Science. The search strategies are checked against a list of core references. A supplementary search is carried out in Google Scholar.
The full search strategies for all data sources will be reported in the publication's supplementary material.

Preliminary search strategy:

1 brain infarction/ or brain stem infarctions/ or cerebral infarction/ or Infarction, Anterior Cerebral Artery/ or Infarction, Middle Cerebral Artery/ or Infarction, Posterior Cerebral Artery/ or ischemic stroke/ or embolic stroke/ or thrombotic stroke/ or stroke, lacunar/ or cerebral small vessel diseases/
2 stroke/ and (asymptomatic diseases/ or (covert or silent or subclinical or sub-clinical or incomplete? or asymptomatic or nonsymptomatic or unsymptomatic or non-symptomatic or unexpected or quiet or symptomfree or symptom-free or symptomless or symptom-less or "free or symptom" or "free of symptoms" or "without symptom?" or occult or incidental or MR-defined or (normal adj1 neurologic*)).ti,ab,kf.)
3 (((covert or silent or subclinical or sub-clinical or incomplete? or asymptomatic or nonsymptomatic or unsymptomatic or non-symptomatic or unexpected or quiet or symptomfree or symptom-free or symptomless or symptom-less or "free of symptom" or "free of symptoms" or "without symptom?" or occult or incidental or MR-defined or identif*) adj3 (ischemi* or ischaemi* or brain or cerebral or cerebrovascular or cerebellar or cortex or cortical or subcortical or hemispher* or lacun* or infarct* or stroke)) or CVBI or CBI or SSBI or "acute brain injury").ti,ab,kf.
4 ((lacun* or (small adj3 (deep or subcortical or vessel))) adj3 (infarct* or stroke*)).ti,ab,kf.
5 or/1-4 [covert brain lesions]
6 exp Hypertension/
7 (hypertens* or normotens*).ti,ab,kf.
8 ((elevated or increased or raised or high or highly or higher or severe or acute* or chronic* or normal or abnormal) adj3 (arterial pressure or blood pressure or bloodpressure or BP or systolic or SBP or diastolic or DBP)).ti,ab,kf.
9 (risk factors/ or ("risk factor" or "risk factors").ti,ab,kf.) and "blood pressure".ti,ab,kf.
10 or/6-9 [hypertension]
11 Magnetic Resonance Imaging/
12 (magnetic resonance imag* or MR imag* or MRI or MR tomograph* or MRT or NMR Imaging? or zeugmatograph* or NMR tomograph* or Proton Spin tomograph* or Magnetization Transfer Contrast Imaging? or Chemical Shift Imaging? or Spin Echo Imaging?).ti,ab,kf.
13 Diffusion Magnetic Resonance Imaging/
14 (diffusion-weighted imag* or DWI or apparent diffusion coefficient or ADC or diffusion restriction).ti,ab,kf.
15 (fluid attenuat* inversion recovery or FLAIR).ti,ab,kf.
16 (((T2? or T1?) adj3 (MRI or weighted or imaging or sequences or hyperintens* or hyper-intens* or hypointens* or hypo-intens* or hypodensit* or hypo-densit*)) or t1w or t2w).ti,ab,kf.
17 or/11-16 [MRI]
18 and/5,10,17 [total results (CBL + HT + MRI)]

Eligible studies identified by screening of the systematic and supplementary search results will be used for citation searching to retrieve additional relevant references.

Participant or population We include studies that enrolled populations comprised adults (≥18 years) with acutely elevated blood pressure or chronic hypertension, including both treated and untreated individuals and that underwent neuroimaging with MRI. Studies including mixed populations are eligible if data for relevant subgroups could be extracted separately.
Studies focusing exclusively on children or adolescents, pregnant populations (e.g., pre-eclampsia/eclampsia), or populations selected primarily based on specific neurological diseases unrelated to hypertension will be excluded.

Intervention
Context:
In the acute setting, we will include studies enrolling adults presenting with markedly elevated blood pressure, including patients with and without evidence of acute target-organ damage. Studies will be eligible provided that no focal neurological deficits suggestive of acute stroke were present at the time of clinical assessment. Accordingly, studies primarily enrolling patients with clinically suspected or overt acute stroke will be excluded.
In the chronic setting, we will include studies enrolling adults with primary arterial hypertension, defined by a documented diagnosis, elevated blood pressure measurements, or the use of antihypertensive medication. Both treated and untreated populations will be eligible, including community-based, outpatient, and hospital-based cohorts with longitudinal follow-up or cross-sectional assessment.

Comparator None reported.

Study designs to be included This review will include observational studies and randomized controlled trials reporting data which allows estimation of the prevalence or incidence of covert brain infarction. Studies will be required to provide sufficient information to derive a numerator (number of individuals with covert brain infarcts) and a corresponding denominator (population at risk). Eligible designs include, but are not limited to, cross-sectional and cohort studies.

Eligibility criteria None reported.

Information sources A systematic literature search will be performed in the following databases: MEDLINE (Ovid), Embase (Ovid) and the Web of Science Core Collection (Web of Science). Google Scholar will be searched for the top 200 hits as a supplementary search (13).

Main outcome(s) The primary outcomes of this review will be the prevalence of (1) acute ischemic lesions in patients with acutely elevated blood pressure and (2) covert brain infarction in populations with chronic hypertension. In the acute setting, acute ischemic lesions will be defined as neuroimaging findings consistent with recent cerebral ischemia, as reported by the original study authors. Where available, information on imaging characteristics suggestive of acute infarction (e.g., diffusion restriction) will be extracted. In populations with chronic hypertension, covert brain infarction will be defined as neuroimaging evidence of prior ischemic tissue injury in the absence of corresponding focal neurological deficits, in accordance with the definition specified in the condition section. Prevalence estimates will be extracted as reported.

Additional outcome(s) Whenever reported, we will extract data for the following outcomes: the distribution of infarct types, including lacunar, small subcortical, and cortical infarcts, prevalence estimates according to clinical setting, including emergency department, inpatient, outpatient, and population-based settings. We will further extract prevalence estimates according to hypertension characteristics, including severity of blood pressure elevation, treated versus untreated hypertension, duration of hypertension, and prevalence estimates stratified by demographic characteristics, including age and sex, where available.

Data management Two reviewers (AZ, JK) will independently screen titles and abstracts for eligibility, followed by independent full-text assessment of potentially relevant studies. Two reviewers (AZ, JK) will independently perform the extraction. Study selection will be managed using Covidence, and data will be extracted into a predefined spreadsheet in Microsoft Excel. Disagreements in screening or data extraction process will be resolved through discussion or by consultation with a third reviewer (BM, TM). The variables for which data will be extracted include population size, population demographics (age, sex) number of covert infarctions, imaging modality, specific imaging finding, infarct type and presumed acuity, study setting, blood pressure definitions, duration of hypertension in the chronic setting, treated vs untreated hypertension.

Quality assessment / Risk of bias analysis The overall certainty of all presented pooled prevalences will be assessed using an adapted Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. As there is no formal guidance for the application of the GRADE approach in prevalence studies (14) we follow the recommendation to apply criteria adapted for prognostic research (15).

Risk of bias will be evaluated at the study level using the JBI critical appraisal tool (11) as this has been formally evaluated and is the most used among prevalence studies. Two reviewers will independently perform the assessments, with disagreements resolved through discussion or consultation with a third reviewer.

Strategy of data synthesis This systematic review will be reported in accordance with the PRISMA statement (15). Data synthesis will be conducted separately for each review objective. For each objective, study characteristics and prevalence estimates will be summarized descriptively. Where sufficient comparative data are available, measures of association reported by individual studies (e.g., odds ratios) will also be summarized descriptively.
Studies will be considered for quantitative synthesis if at least three studies are found to be similar in terms of population and outcome definition. Quantitative synthesis of the reported prevalences will be performed using random-effects meta-analysis of proportions. Due to the bounded nature and variance instability of prevalence data, pooled estimates will be calculated using the Freeman–Tukey double arcsine transformation (16). Statistical heterogeneity will be evaluated using I^2 statistic and between-study variance (τ^2). Analyses will be performed using Stata/MP 18.0 for Mac (Apple Silicon) (StataCorp, 2023) and Stata's meta command.
Meta-analysis will not be performed if studies are considered clinically or methodologically too heterogeneous with respect to population characteristics, imaging modality, or outcome

definition, or if fewer than three comparable studies are available. In such cases, findings will be synthesized narratively.

Subgroup analysis Where sufficient data are available, sources of heterogeneity in prevalence estimates will be explored using prespecified subgroup analyses and meta-regression. As a first step, analyses will be stratified according to studies of acute blood pressure elevation and studies of chronic blood pressure elevation. Further analyses within each stratum will depend on the type of covariate, consistency of reporting, and number of available studies.

For studies of acute blood pressure elevation or hypertensive crisis, prespecified covariates will include hypertensive emergency versus hypertensive urgency, timing of neuroimaging, severity of blood pressure elevation, patient selection method, age distribution, sex distribution, and lesion characteristics, including cortical, subcortical, lacunar, or multiple acute ischemic lesions.

For studies of chronic blood pressure elevation or chronic hypertension, prespecified covariates will include hypertension definition and severity, controlled versus uncontrolled hypertension, treated versus untreated hypertension, duration of hypertension or time since diagnosis, clinical setting, geographic region, age distribution, and sex distribution.

For categorical covariates, subgroup analyses will be the primary approach. Studies will be grouped according to prespecified categories, and pooled prevalence estimates will be calculated within each subgroup where at least three studies are available per subgroup. Examples of categorical covariates include clinical setting, patient selection method, imaging modality, and hypertensive emergency versus hypertensive urgency.

For continuous covariates, including age, blood pressure, time from presentation to imaging, and duration of hypertension, random-effects meta-regression will use study-level summary values. Means will be used preferentially; where means are unavailable, medians will be used as the available study-level estimate. If meta-regression is not feasible because fewer than 10 studies are available for a covariate or because reporting is inconsistent, continuous covariates may be categorized using clinically meaningful thresholds and explored through subgroup analyses, provided that at least three studies are available per subgroup.

Meta-regression will be performed only when at least 10 studies are available for the respective covariate. To avoid overfitting, each meta-regression model will include one covariate at a time. Because meta-regression is based on study-level data, findings will be interpreted as exploratory and with caution.

If neither subgroup analysis nor meta-regression is feasible because of limited data, inconsistent reporting, or substantial clinical heterogeneity, potential sources of heterogeneity will be summarized narratively. Outcome measures other than the prevalence of covert brain infarction, including reported effect estimates for associations between blood pressure elevation and covert brain infarction, will also be summarized narratively where quantitative synthesis is not appropriate.

Sensitivity analysis Sensitivity analyses will be performed to evaluate the robustness of the results by excluding studies at high risk of bias, restricting to studies published only in the last ten years (evaluating the effect of technical advances), comparing fixed-effect with random-effects models, and using logit transformation.

Language restriction Articles in any languages will be screened based on English abstracts and included when translation is feasible.

Country(ies) involved The systematic review is conducted in Switzerland.

Keywords Hypertension; blood pressure; hypertensive emergency; hypertensive urgency; silent stroke; covert infarction; silent brain infarct; magnetic resonance imaging; neuroimaging.

Dissemination plans The results of this systematic review will be submitted for publication in a peer-reviewed journal and presented at relevant national and international scientific conferences.

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