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Cardiac complications of stroke: protocol for a systematic review and meta-analysis

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Cardiac complications of stroke: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

Stroke is the second most common cause of death after ischaemic heart diseases and the third leading cause of disability worldwide. The contribution of cardiac complications to the mortality of patients with stroke is variable across studies, ranging from 12.5% to 22.7%. Many of these cardiac complications are preventable, and early recognition and adequate management guided by appropriate up-to-date knowledge of their relative incidence and fatality can help to improve patients' outcome. This systematic review aims to summarize the available data on the burden of cardiac complications of stroke.

Methods and analysis

This review will include all cross-sectional, case-controls and cohort studies and clinical trials conducted between January 01, 1950 and December 31, 2017, involving adults and/or children, and reporting on the prevalence, the incidence and/or the mortality of cardiac complications of stroke. Two reviewers will independently screen titles and abstracts of records retrieved from PubMed, Excerpta Medica Database, ISI Web of Science and the Cumulative Index to Nursing and Allied Health for eligibility, and then assess the risk of bias and quality of reporting to select the studies which will be included. All authors will contribute to the retrieval of full-texts of eligible records and data extraction. Heterogeneity across studies will be evaluated by the $\chi 2$ test on Cochrane's Q statistic. Study-specific estimates of the prevalence, incidence and mortality of cardiac complications of stroke across studies will be pooled through random-effect or fixed-effect meta-analysis depending on the source of the heterogeneity, after stabilizing the variance of individual studies using the

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Freeman-Tukey double arc-sine transformation. Visual analysis of funnel plot and Egger's test will be done to detect small study effect.

Ethics and dissemination

This review and meta-analysis will be based on published data and will therefore not require a specific ethics clearance. The results will be published in peer-reviewed journals.

Study registration number: PROSPERO CRDXXX (pending).

STRENGTHS AND LIMITATIONS OF THE REVIEW

- This review will provide an up-to-date summary of the burden of cardiac complications of stroke, reflecting the changes in diagnosis and management of stroke and cardiac diseases over the past decades.
- We will use robust meta-analysis tools to provide reliable estimates of the prevalence, incidence, and mortality of cardiac complications of acute stroke.
- One major limitation could be the predominance of data from randomized clinical trials known to recruit healthier patients and this might underestimate the real-world incidence of cardiac complications of stroke.

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INTRODUCTION

Stroke is the second most common cause of death after ischaemic heart diseases and the third leading cause of disability worldwide [1-3]. Between 1990 and 2010, the burden of ischaemic and haemorrhagic stroke increased significantly in terms of the absolute number of people with incident ischaemic and haemorrhagic stroke (37% and 47% increase, respectively), number of deaths (21% and 20% increase), and disability-adjusted life years lost (18% and 14% increase) [4]. In 2015, the number of stroke-related deaths was estimated to 6.7 million [5]. The initial neurologic injury is responsible for the death in up to 43.9% of cases [6]. The contribution of cardiac complications to the mortality of patients with stroke is variable across studies, ranging from 12.5% to 22.7% [6-8]. Data from the Virtual International Stroke Trials Archive (VISTA) reveal that most serious cardiac complications occur within the first 14 days after stroke [6]. They can arise as a direct consequence of the brain injury itself, from the ensuing reduction in mobility, or from stroke-related treatments [9]. The spectrum of abnormalities includes hypertension, hypotension, myocardial infarction, repolarization abnormalities, cardiac arrhythmias, left ventricular (LV) dysfunction, and cardiac arrest [10, 11]. Many of these cardiac complications are preventable and when this is not possible, early recognition and treatment can improve patients outcome [9].

In 2005, a systematic review on the risk of myocardial infarction and non-stroke vascular death after transient ischaemic attack (TIA) and ischaemic stroke revealed an annual risk of 2.2% (1.7 to 2.7) for total myocardial infarction, 0.9% (0.7 to 1.2) for nonfatal myocardial infarction and 1.1% (0.8 to 1.5) for fatal myocardial infarction [12]. However, the review did not consider other non-fatal cardiac complications of stroke. Furthermore, since the publication of this systematic review, the management of patients with stroke has changed dramatically to include earlier, longer and often more invasive cardiac monitoring [13, 14], earlier and more aggressive treatment with thrombolysis and antithrombotics [15-17],

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increased availability of percutaneous coronarography intervention, which all might have changed the incidence and the mortality of cardiac complications of acute stroke. Here, we propose a protocol for a systematic review which aims at summarizing the available data on the burden of cardiac complications of stroke.

REVIEW QUESTION

What is the burden of cardiac complications of stroke?

OBJECTIVES

To determine:

- The prevalence and the incidence of cardiac complications of stroke
- The mortality rate of these complications

METHODS

This review protocol has been prepared according to the 2015 Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines (checklist provided as appendix 1) [19]. The review is registered in the PROSPERO International Prospective Register for systematic reviews, registration number CRDXXX (pending).

1. Criteria for considering studies for the review

Inclusion criteria

We will include all cross-sectional, case-controls and cohort studies and clinical trials conducted between January 01, 1950 and December 31, 2017, involving adults and/or children, and reporting on the prevalence, the incidence or the mortality of cardiac complications of stroke or enough data to compute these estimates. No language restriction will be applied.

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Exclusion criteria

We will exclude reviews, commentaries, editorials, studies will small sample size (less than 30 participants), and studies lacking primary data or with incomplete methods description. For studies leading to more than one publication (duplicates), only the most comprehensive report including the largest sample size will be considered.

2. Search strategy for the identification of relevant studies

A comprehensive literature search will be performed in PubMed, Excerpta Medica Database (EMBASE), ISI Web of Science (Science Citation Index), and the Cumulative Index to Nursing and Allied Health (CINHAL) to identify potentially eligible studies. The literature search strategy is summarized in Table 1 and Table 2 for PubMed and EMBASE, respectively. Following the search in databases, we will screen the reference lists of eligible articles and relevant reviews as well as conference proceedings to identify additional sources of information. Search results will be compiled using the citation management software EndNote X6.0.1. The proposed start date for this review is 01st January 2017 and it is expected to be completed in a maximum of 6 months.

3. Selection of studies for inclusion in the review

Titles and abstracts of records identified through literature search will be independently screened for eligibility by two members of the research team (GHKD and JKT). Full-texts of records deemed eligible will be retrieved and further assessed for inclusion by the same investigators. A screening guide will be developed to ensure consistency of the screening method applied by both assessors. Any disagreement will be resolved by discussion and consensus. If the latter is not reached, arbitration will be sought from a third member of the team (JJN). The interrater agreement for the selection of studies will be assessed using a non-weighted Cohen's kappa statistic [18, 19]. Authors of publications reporting unclear data that

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may be subject to multiple interpretations will be contacted by email for clarification or to request supplemental information. If a study is excluded, the reasons will be documented.

4. Assessment of the methodological quality and risk of bias

The Risk of Bias Tool for Prevalence Studies [20] and the Cochrane Risk of Bias Tool for randomized control trials [21] will be used to evaluate the methodological quality and risk of bias for each study using the full-text publication. The quality of reporting of the studies included will be assessed using either the STROBE or the CONSORT checklist depending on the nature of the study (observational study or clinical trial) [22, 23]. Risk of bias and quality of reporting scores will be presented in a table and interrater agreement will be assessed using a weighted Cohen's kappa statistic [24, 25].

5. Data extraction and management

A standardized data extraction sheet will be used to collect information on:

- Study identification: first author's name, year of publication, period of recruitment of participants, country.
- Study and participants' characteristics: study design (cross-sectional, cohort, case-control, clinical trial), setting (hospital-based, community-based), sample size, mean or median age, age range, proportions of male participants, proportion of patients with pre-existing cardiovascular risk factors (hypertension, diabetes mellitus, obesity, dyslipidaemia) or diseases (coronary artery disease, heart failure, previous stroke), mean or median stroke severity score on the National Institute of Health Stroke Scale, proportion of patients with each type of cerebrovascular disease (ischaemic stroke, intracranial haemorrhage, subarachnoid haemorrhage), proportion of patients with lesion of the insula (if reported), proportion of patients with right hemisphere lesion (if

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reported), diagnostic criteria for stroke, proportion of patients who received intravenous thrombolysis, duration of follow-up for cohort studies and clinical trials.

- Epidemiologic estimates: prevalence, incidence, and mortality of cardiac complications of stroke. Whenever these estimates are not readily available or computable using primary data in the publication, the corresponding author will be contacted to request the missing information. The definition and diagnostic criteria for each cardiac complication will also be reported.

6. Data analysis and reporting

Data will be analyzed using the metaprop command provided with the software STATA (version 13, StataCorp, College Station, TX, USA) [26]. Heterogeneity will be evaluated by the $\chi 2$ test on Cochrane's Q statistic and quantified using I^2 values, considering that I^2 values of 25%, 50% and 75%, represent low, medium and high heterogeneity respectively [27]. Subgroup analyses will be performed to detect its possible sources. Depending on whether the heterogeneity between effect estimates is most likely due to clinical or methodological diversity between studies, or due to random variation, study-specific estimates of the prevalence, incidence and mortality of cardiovascular complications of stroke across studies will be pooled through fixed-effect or random effect meta-analysis respectively, after stabilizing the variance of individual studies using the Freeman-Tukey double arc-sine transformation [28, 29]. Study-specific estimates will be determined from the point estimate and the appropriate denominators, assuming a binominal distribution. Visual analysis of funnel plot and Egger's test will be done to detect small-study effect [30]. All tests will be two-sided and statistical significance will be defined as $p < 0.05$.

The results of this systematic review will be reported according to the MOOSE guidelines [31]. The study selection process will be summarized using a flow diagram. Reasons for study

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exclusion will be described. Quantitative data will be presented in summary tables and forest plots where appropriate.

7. Potential amendments

We do not intend to make any amendment to this protocol. However, any necessary amendment will be documented and reported transparently.

8. Ethics and dissemination

This systematic review and meta-analysis will be based on published data and therefore will not require a specific ethics clearance. The results will be published in peer-reviewed journals and further presented at conferences. The review will be updated regularly as new data become available.

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CONFLICTS OF INTEREST: The authors declare that they have no conflict of interest.

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Table 1: Search strategy for PubMed

	Search terms
#1	"Stroke"[Tiab] OR "Transient ischemic attack"[Tiab] OR "TIA"[Tiab] OR "Intracranial hemorrhage"[Tiab] OR "Intracranial haemorrhage"[Tiab] OR "Subarachnoid hemorrhage"[Tiab] OR "Subarachnoid haemorrhage"[Tiab] OR "cerebrovascular accident"[Tiab]
#2	"Myocardial infarction"[Tiab] OR "acute coronary syndrome" [tiab] OR "myocardial ischaemia" [tiab] OR "Takotsubo"[Tiab] OR "Wall motion abnormalities"[Tiab] OR "Neurogenic cardiac damage"[Tiab] OR "Arrhythmia"[Tiab] OR "atrioventricular block" [tiab] OR "sinoatrial block" [tiab] OR "atrial flutter" [tiab] OR "supraventricular tachycardia" [tiab] OR "ventricular tachycardia" [tiab] OR "Atrial fibrillation"[Tiab] OR "QT prolongation" [tiab] OR "torsade de pointes" [tiab] OR "hypertension" [tiab] OR "hypotension" [tiab]
#3	"Mortality"[Tiab] OR "Death"[Tiab] OR "Fatality"[Tiab] OR "Prevalence"[Tiab] OR "Incidence"[Tiab] OR "Outcome"[Tiab]
#4	#1 AND #2 AND #3
#5	Restrict [humans]

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Table 2: Search strategy for EMBASE

	Search tems
#1	("cerebrovascular accident"/exp OR "cerebrovascular accident":ti,ab OR "stroke":ti,ab) OR ("brain hemorrhage"/exp OR "brain hemorrhage":ti,ab OR "intracranial hemorrhage":ti,ab)
#2	“hypertension” :ti,ab OR “hypotension” :ti,ab OR 'heart infarction':ti,ab OR 'myocardial infarction':ti,ab OR 'acute coronary syndrome':ti,ab OR 'heart muscle ischemia':ti,ab OR 'myocardial ischemia':ti,ab OR 'takotsubo':ti,ab OR 'wall motion abnormalit*':ti,ab OR 'neurogenic cardiac damage':ti,ab OR 'atrioventricular block':ti,ab OR 'sinoatrial block':ti,ab OR 'atrial flutter':ti,ab OR 'supraventricular tachycardia':ti,ab OR 'ventricular tachycardia':ti,ab OR 'atrial fibrillation':ti,ab OR 'qt prolongation':ti,ab
#3	“death”:ti,ab OR “Fatality”/exp OR “Fatal*”:ti,ab OR “lethality”/exp OR “lethal*”:ti,ab)
#4	#1 AND #2 AND #3
#6 (Restrict to humans)	#5 AND 'human'/de
#7 (Filter by study type)	#6 AND ('clinical study'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'family study'/de OR 'major clinical study'/de OR 'medical record review'/de OR 'observational study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de OR 'systematic review'/de)

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Keywords:	Stroke < NEUROLOGY, cardiac complications, Epidemiology < TROPICAL MEDICINE, Systematic review, Mortality

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ABSTRACT

Introduction

Stroke is the second most common cause of death after ischaemic heart diseases and the third leading cause of disability worldwide. The contribution of cardiac complications to the mortality of patients with stroke is variable across studies, ranging from 12.5% to 22.7%. Many of these cardiac complications are preventable, and early recognition and adequate management guided by appropriate up-to-date knowledge of their relative incidence and fatality can help to improve patients' outcome. This systematic review aims to summarize the available data on the burden of cardiac complications after stroke.

Methods and analysis

This review will include all cross-sectional, case-controls and cohort studies and clinical trials published between January 01, 1950 and December 31, 2017, involving adults and/or children, and reporting on the prevalence, the incidence and/or the mortality of cardiac complications after stroke. Two reviewers will independently screen titles and abstracts of records retrieved from PubMed, Excerpta Medica Database, ISI Web of Science and the Cumulative Index to Nursing and Allied Health for eligibility, and then assess the risk of bias and quality of reporting to select the studies which will be included. All authors will contribute to the retrieval of full-texts of eligible records and data extraction. Heterogeneity across studies will be evaluated by the $\chi 2$ test on Cochrane's Q statistic. Study-specific estimates of the prevalence, incidence and mortality of cardiac complications after stroke across studies will be pooled through random-effect or fixed-effect meta-analysis depending on the source of the heterogeneity, after stabilizing the variance of individual studies using the

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Freeman-Tukey double arc-sine transformation. Visual analysis of funnel plot and Egger's test will be done to detect small study effect.

Ethics and dissemination

This review and meta-analysis will be based on published data and will therefore not require a specific ethics clearance. The results will be published in peer-reviewed journals.

Study registration number: PROSPERO CRD42018082551.

STRENGTHS AND LIMITATIONS OF THE REVIEW

- This review will provide an up-to-date summary of the burden of cardiac complications after stroke, reflecting the changes in diagnosis and management of stroke and cardiac diseases over the past decades.
- We will use robust meta-analysis tools to provide reliable estimates of the prevalence, incidence, and mortality of cardiac complications after acute stroke.
- One major limitation could be the predominance of data from randomized clinical trials known to recruit healthier patients and this might underestimate the real-world incidence of cardiac complications after stroke.

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INTRODUCTION

Stroke is the second most common cause of death after ischaemic heart diseases and the third leading cause of disability worldwide [1-3]. Between 1990 and 2010, the burden of ischaemic and haemorrhagic stroke increased significantly in terms of the absolute number of people with incident ischaemic and haemorrhagic stroke (37% and 47% increase, respectively), number of deaths (21% and 20% increase), and disability-adjusted life years lost (18% and 14% increase) [4]. In 2015, the number of stroke-related deaths was estimated to 6.7 million [5]. The initial neurologic injury is responsible for the death in up to 43.9% of cases [6]. The contribution of cardiac complications to the mortality of patients with stroke is variable across studies, ranging from 12.5% to 22.7% [6-8]. Data from the Virtual International Stroke Trials Archive (VISTA) reveal that most serious cardiac complications occur within the first 14 days after stroke [6]. They can arise as a direct consequence of the brain injury itself, from the ensuing reduction in mobility, or from stroke-related treatments [9]. The spectrum of abnormalities includes hypertension, hypotension, myocardial infarction, repolarization abnormalities, cardiac arrhythmias, left ventricular (LV) dysfunction, and cardiac arrest [10, 11]. Many of these cardiac complications are preventable and when this is not possible, early recognition and treatment can improve patients outcome [9].

In 2005, a systematic review on the risk of myocardial infarction and non-stroke vascular death after transient ischaemic attack (TIA) and ischaemic stroke revealed an annual risk of 2.2% (1.7 to 2.7) for total myocardial infarction, 0.9% (0.7 to 1.2) for nonfatal myocardial infarction and 1.1% (0.8 to 1.5) for fatal myocardial infarction [12]. However, the review did not consider other non-fatal cardiac complications after stroke. Furthermore, since the publication of this systematic review, the management of patients with stroke has changed dramatically to include earlier, longer and often more invasive cardiac monitoring [13, 14], earlier and more aggressive treatment with thrombolysis and antithrombotics [15-17],

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increased availability of percutaneous coronarography intervention, which all might have changed the incidence and the mortality of cardiac complications after acute stroke. Here, we propose a protocol for a systematic review which aims at summarizing the available data on the burden of cardiac complications after stroke.

REVIEW QUESTION

What is the burden of cardiac complications after stroke?

OBJECTIVES

To determine:

- The prevalence and the incidence of cardiac complications after stroke
- The mortality rate of these complications

METHODS

This review protocol has been prepared according to the 2015 Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines (checklist provided as appendix 1) [18]. The review is registered in the PROSPERO International Prospective Register for systematic reviews, registration number CRD42018082551.

1. Criteria for considering studies for the review

Inclusion criteria

We will include all cross-sectional, case-controls and cohort studies and clinical trials published between January 01, 1950 and December 31, 2017, involving adults and/or children, and reporting on the prevalence, the incidence or the mortality of cardiac complications after stroke or enough data to compute these estimates. No language restriction will be applied.

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Exclusion criteria

We will exclude reviews, commentaries, editorials, studies will small sample size (less than 30 participants), and studies lacking primary data or with incomplete methods description. For studies leading to more than one publication (duplicates), only the most comprehensive report including the largest sample size will be considered.

2. Search strategy for the identification of relevant studies

A comprehensive literature search will be performed in PubMed, Excerpta Medica Database (EMBASE), ISI Web of Science (Science Citation Index), and the Cumulative Index to Nursing and Allied Health (CINHAL) to identify potentially eligible studies. The literature search strategy is summarized in Table 1 and Table 2 for PubMed and EMBASE, respectively. Following the search in databases, we will screen the reference lists of eligible articles and relevant reviews as well as conference proceedings to identify additional sources of information. Search results will be compiled using the citation management software EndNote X6.0.1. The proposed start date for this review is 01st January 2018 and it is expected to be completed in a maximum of 6 months.

3. Selection of studies for inclusion in the review

Titles and abstracts of records identified through literature search will be independently screened for eligibility by two members of the research team (GHKD and JKT). Full-texts of records deemed eligible will be retrieved and further assessed for inclusion by the same investigators. A screening guide will be developed to ensure consistency of the screening method applied by both assessors. Any disagreement will be resolved by discussion and consensus. If the latter is not reached, arbitration will be sought from a third member of the team (JJN). The interrater agreement for the selection of studies will be assessed using a non-weighted Cohen's kappa statistic [19, 20]. Authors of publications reporting unclear data that

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may be subject to multiple interpretations will be contacted by email for clarification or to request supplemental information. If a study is excluded, the reasons will be documented.

4. Assessment of the methodological quality and risk of bias

The Risk of Bias Tool for Prevalence Studies [21] and the Cochrane Risk of Bias Tool for randomized control trials [22] will be used to evaluate the methodological quality and risk of bias for each study using the full-text publication. The quality of reporting of the studies included will be assessed using either the STROBE or the CONSORT checklist depending on the nature of the study (observational study or clinical trial) [23, 24]. Risk of bias and quality of reporting scores will be presented in a table and interrater agreement will be assessed using a weighted Cohen's kappa statistic [25, 26].

5. Data extraction and management

A standardized data extraction sheet will be used to collect information on:

- Study identification: first author's name, year of publication, period of recruitment of participants, country.
- Study and participants' characteristics: study design (cross-sectional, cohort, case-control, clinical trial), setting (hospital-based, community-based), sample size, mean or median age, age range, proportions of male participants, proportion of patients with pre-existing cardiovascular risk factors (hypertension, diabetes mellitus, obesity, dyslipidaemia) or diseases (coronary artery disease, heart failure, previous stroke), mean or median stroke severity score on the National Institute of Health Stroke Scale, proportion of patients with each type of cerebrovascular disease (ischaemic stroke, intracranial haemorrhage, subarachnoid haemorrhage), proportion of patients with lesion of the insula (if reported), proportion of patients with right hemisphere lesion (if reported), diagnostic criteria for stroke, proportion of patients who received

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intravenous thrombolysis, proportion of patients who received endovascular thrombectomy (without or with prior thrombolysis), mean (or median) time to the diagnosis of the complications reported (if available), duration of follow-up for cohort studies and clinical trials.

- Epidemiologic estimates: prevalence, incidence, and mortality of cardiac complications after stroke. Whenever these estimates are not readily available or computable using primary data in the publication, the corresponding author will be contacted to request the missing information. The definition and diagnostic criteria used for each cardiac complication will also be reported. An illustrative list of the cardiac complications that will be considered in this review is provided in Table 3.

6. Data analysis and reporting

Data will be analyzed using the metaprop command provided with the software STATA (version 13, StataCorp, College Station, TX, USA) [27]. Heterogeneity will be evaluated by the $\chi 2$ test on Cochrane's Q statistic and quantified using I^2 values, considering that I^2 values of 25%, 50% and 75%, represent low, medium and high heterogeneity respectively [28]. Subgroup analyses will be performed to detect its possible sources. Depending on whether the heterogeneity between effect estimates is most likely due to clinical or methodological diversity between studies, or due to random variation, study-specific estimates of the prevalence, incidence and mortality of cardiovascular complications after stroke across studies will be pooled through fixed-effect or random effect meta-analysis respectively, after stabilizing the variance of individual studies using the Freeman-Tukey double arc-sine transformation [29, 30]. Study-specific estimates will be determined from the point estimate and the appropriate denominators, assuming a binominal distribution. Visual analysis of

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funnel plot and Egger's test will be done to detect small-study effect [31]. All tests will be two-sided and statistical significance will be defined as $p < 0.05$.

The results of this systematic review will be reported according to the MOOSE guidelines [32]. The study selection process will be summarized using a flow diagram. Reasons for study exclusion will be described. Quantitative data will be presented in summary tables and forest plots where appropriate.

7. Potential amendments

We do not intend to make any amendment to this protocol. However, any necessary amendment will be documented and reported transparently.

8. Ethics and dissemination

This systematic review and meta-analysis will be based on published data and therefore will not require a specific ethics clearance. The results will be published in peer-reviewed journals and further presented at conferences. The review will be updated regularly as new data become available.

ACKNOWLEDGEMENTS: None

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AUTHORS CONTRIBUTIONS: GHKD, JKT and JJN conceived the study. GHKD and JKT drafted the manuscript. SRN, CMFD, GHKD, JKT, JGZ and JJN revised the manuscript. All authors approved the final version. JKT is the guarantor of the review.

CONFLICTS OF INTEREST: The authors declare that they have no conflict of interest.

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Table 1: Search strategy for PubMed

	Search terms
#1	"Stroke"[Tiab] OR "Transient ischemic attack"[Tiab] OR "TIA"[Tiab] OR "Intracranial hemorrhage"[Tiab] OR "Intracranial haemorrhage"[Tiab] OR "Subarachnoid hemorrhage"[Tiab] OR "Subarachnoid haemorrhage"[Tiab] OR "cerebrovascular accident"[Tiab]
#2	"Myocardial infarction"[Tiab] OR “acute coronary syndrome” [tiab] OR “myocardial ischaemia” [tiab] OR "Takotsubo"[Tiab] OR "Wall motion abnormalities"[Tiab] OR "Neurogenic cardiac damage"[Tiab] OR "Arrhythmia"[Tiab] OR “atrioventricular block” [tiab] OR “sinoatrial block” [tiab] OR “atrial flutter” [tiab] OR “supraventricular tachycardia” [tiab] OR “ventricular tachycardia” [tiab] OR "Atrial fibrillation"[Tiab] OR “QT prolongation” [tiab] OR “torsade de pointes” [tiab] OR “hypertension” [tiab] OR “hypotension” [tiab]
#3	"Mortality"[Tiab] OR "Death"[Tiab] OR "Fatality"[Tiab] OR "Prevalence"[Tiab] OR "Incidence"[Tiab] OR "Outcome"[Tiab]
#4	#1 AND #2 AND #3
#5	Restrict [humans]

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Table 2: Search strategy for EMBASE

	Search tems
#1	("cerebrovascular accident"/exp OR "cerebrovascular accident":ti,ab OR "stroke":ti,ab) OR ("brain hemorrhage"/exp OR "brain hemorrhage":ti,ab OR "intracranial hemorrhage":ti,ab)
#2	“hypertension” :ti,ab OR “hypotension” :ti,ab OR 'heart infarction':ti,ab OR 'myocardial infarction':ti,ab OR 'acute coronary syndrome':ti,ab OR 'heart muscle ischemia':ti,ab OR 'myocardial ischemia':ti,ab OR 'takotsubo':ti,ab OR 'wall motion abnormalit*':ti,ab OR 'neurogenic cardiac damage':ti,ab OR 'atrioventricular block':ti,ab OR 'sinoatrial block':ti,ab OR 'atrial flutter':ti,ab OR 'supraventricular tachycardia':ti,ab OR 'ventricular tachycardia':ti,ab OR 'atrial fibrillation':ti,ab OR 'qt prolongation':ti,ab
#3	“death”:ti,ab OR “Fatality”/exp OR “Fatal*”:ti,ab OR “lethality”/exp OR “lethal*”:ti,ab)
#4	#1 AND #2 AND #3
#6 (Restrict to humans)	#5 AND 'human'/de
#7 (Filter by study	#6 AND ('clinical study'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de

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type)	OR 'family study'/de OR 'major clinical study'/de OR 'medical record review'/de OR 'observational study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de OR 'systematic review'/de)

Table 3: List of possible cardiac complications after stroke

Acute coronary syndromes	Myocardial infarction
	Regional wall motion abnormality without infarction / neurogenic cardiac damage / Takotsubo cardiomyopathy
Repolarization abnormalities	Abnormal waves and segments
	ST elevation
	T waves (inversion or abnormal shape)
	U waves
	Q waves
	QT prolongation
Arrhythmias	Atrial fibrillation
	Atrial flutter
	Supraventricular tachycardia
	Ventricular tachycardia
	Torsade de pointe
	Sinoatrial block
	Atrioventricular block
	Bundle block
Elevated cardiac enzymes	Troponin
	Creatinine kinase-MB
	Atrial natriuretic peptide
Others	Sudden cardiac death
	Hypertension
	Hypotension

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Pending
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review.	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	12
Study records:			

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Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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