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

Guidelle Héloïse Kenmogne-Domning,[1] Joseph Kamtchum-Tatuene,[2,3] Steve Raoul Noumegni,[4] Christophe Maxime Fokoua-Dongmo,[5] Joseline Guetsop Zafack,[6] Jean Jacques Noubiap[7]

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For numbered affiliations see end of article.

Correspondence to
Dr Joseph Kamtchum-Tatuene;
jkamtchum@yahoo.fr

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' outcomes. This systematic review aims to summarise the available data on the burden of cardiac complications after stroke.

Methods and analysis This review will include all cross-sectional, case–control and cohort studies and clinical trials published between 1 January 1950 and 31 December 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 Literature 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 χ^2 test on Cochran'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 stabilising the variance of individual studies using the Freeman-Tukey double arcsine transformation. Visual analysis of funnel plots 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 ethical clearance. The results will be published in peer-reviewed journals.

PROSPERO registration number CRD42018082551.

INTRODUCTION

Stroke is the second most common cause of death after ischaemic heart diseases and the third leading cause of disability worldwide.[1–3]

Strengths and limitations of this study

► 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 randomised controlled trials which are known to recruit healthier patients, and this might underestimate the real-world incidence of cardiac complications after stroke.

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), the number of deaths (21% and 20% increase) and disability-adjusted life years (18% and 14% increase).[4] In 2015, the number of stroke-related deaths was estimated to be 6.7 million.[5] The initial neurological 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 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, repolarisation abnormalities, cardiac arrhythmias, left ventricular 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' outcomes.[9]

In 2005, a systematic review of the risk of myocardial infarction and non-stroke vascular death after transient ischaemic attack and ischaemic stroke revealed an annual risk of 2.2% (1.7–2.7) for total myocardial infarction, 0.9% (0.7–1.2) for non-fatal myocardial infarction and 1.1% (0.8–1.5) 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] 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 summarising 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 Reviews and Meta-Analyses Protocols guidelines (checklist provided as online supplementary appendix).[18] The review is registered in the International Prospective Register for Systematic Reviews (registration number CRD42018082551).

Criteria for considering studies for the review

Inclusion criteria

We will include all cross-sectional, case–control and cohort studies and clinical trials published between 1 January 1950 and 31 December 2017, involving adults and/or children, and reporting on the prevalence, the incidence or the mortality of cardiac complications after stroke or providing enough data to compute these estimates. No language restriction will be applied.

Exclusion criteria

We will exclude reviews, commentaries, editorials, studies with 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.

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 Literature to identify potentially eligible studies. The literature search strategy is summarised 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 1 January 2018 and it is expected to be completed in a maximum of 6 months.

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 (GHK-D and JK-T). 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.

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]

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)

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 inter-rater 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 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.

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 randomised controlled 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 Strengthening the Reporting of Observational Studies in Epidemiology or the Consolidated Standards of Reporting Trials 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 inter-rater agreement will be assessed using a weighted Cohen's kappa statistic.[25 26]

Data extraction and management

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

► Epidemiological estimates: prevalence, incidence and mortality of cardiac complications after stroke. Whenever these estimates are not readily available or computable using the 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.

Data analysis and reporting

Data will be analysed using the metaprop command provided with the software STATA (V.13, StataCorp).[27] Heterogeneity will be evaluated by the χ^2 test on Cochran's Q statistic and quantified using I² values, considering that I² values of 25%, 50% and 75%, represent low, medium and high heterogeneity, respectively.[28] Subgroup analyses will be performed to detect possible sources of heterogeneity. 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

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
Repolarisation 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
	Creatine kinase-MB
	Atrial natriuretic peptide
Others	Sudden cardiac death
	Hypertension
	Hypotension

complications after stroke across studies will be pooled through fixed-effect or random-effect meta-analysis, respectively, after stabilising the variance of individual studies using the Freeman-Tukey double arcsine transformation.[29] [30] Study-specific estimates will be determined from the point estimate and the appropriate denominators, assuming a binominal distribution. Visual analysis of funnel plots 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 Meta-analysis Of Observational Studies in Epidemiology guidelines.[32] The study selection process will be summarised using a flow diagram. Reasons for study exclusion will be described. Quantitative data will be presented in summary tables and forest plots where appropriate.

Patient and Public Involvement statement
No patients were involved in this study.

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

Ethics and dissemination
This systematic review and meta-analysis will be based on published data and therefore will not require a specific ethical 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.

Author affiliations
[1]Higher Institute of Health Sciences, Universite des Montagnes, Bangangté, Cameroon
[2]Malawi-Liverpool-Wellcome Trust Clinical Research Programme, University of Malawi College of Medicine, Blantyre, Malawi
[3]Brain Infections Group, Institute of Infection and Global Health, University of Liverpool, Liverpool, UK
[4]Department of Public Health, Paris-Sud Faculty of Medicine, University of Paris-Saclay, Paris, France
[5]School of Public Health, University at Albany, State University of New York, Albany, New York, USA
[6]Department of Social and Preventive Medicine, Laval University, Quebec, Canada
[7]Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa

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