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Atrial fibrillation among adults with heart failure in sub-Saharan Africa; prevalence, incidence and all-cause mortality: a systematic review and meta-analysis protocol

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Complete List of Authors:	Agbor, Ndip; Ibal sub-Divisional Hospital, General practice Aminde, Leopold; Clinical Research Education, Networking & Consultancy (CRENC), Douala, Frank Leonel, Tianyi Tianyi; Mayo Darle sub-Divisional Hospital, Mbanga, Clarence; Mankon Sub-divisional Hospital Petnga, Saint Just; Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Public Health Ditah, chobufo Noubiap, Jean Jacques; Edea Regional Hospital, Internal Medicine Unit
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Atrial fibrillation among adults with heart failure in sub-Saharan Africa; prevalence, incidence and all-cause mortality: a systematic review and meta-analysis protocol

Authors: Valirie Ndip Agbor[1*]; Leopold Ndemnge Aminde[2,3]; Frank-Leonel Tianyi[4]; Clarence Mvalo Mbanga[5]; Saint-Juste N. Petnga[6]; Chobufo Ditah[7]; Jean Jacques Noubiap[8]

Affiliations: [1] Ibal Sub-divisional Hospital, Oku, Cameroon; [2] Non-communicable disease unit, Clinical Research Education, Networking and Consultancy (CRENC), Douala, Cameroon; [3] School of Public Health, Faculty of Medicine, University of Queensland, Brisbane, Australia; [4] Mayo-Darle sub-Divisional Hospital, Banyo, Adamawa Region, Cameroon; [5]Mankon sub-divisional Hospital, Bamenda, North-west Region, Cameroon; [6] Department of Public Health, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Yaoundé, Cameroon; [7] Doctors Without Borders-French Section (MSF-F), France; [8] Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa.

Email addresses: VNA: nvagbor@gmail.com; LNA: amindeln@gmail.com; FLT: tianyifrankleonel@gmail.com; CMM: mbangaclarence@gmail.com; SNP: p.ngass@gmail.com; CD: ditahdivine@yahoo.co.uk; JJN: noubiapjj@yahoo.fr

***Corresponding author:** Dr. Valirie Ndip Agbor, Ibal sub-Divisional Hospital, Oku, North-west Region, Cameroon. Tel: 00 237 676546548, Email: nvagbor@gmail.com;

Keywords: Prevalence, incidence, mortality, atrial fibrillation, heart failure, sub-Saharan Africa

Abstract

Introduction: Heart failure (HF) remains a major non-communicable disease in sub-Saharan Africa (SSA) associated with high rates of readmission, mortality and loss of economic productivity as it affects mostly young and active adults. Atrial fibrillation is a major determinant of mortality among patients with HF in SSA. Meanwhile, the use of anti-arrhythmic medications in the region remains unacceptably low. This review aims to evaluate the prevalence, incidence and all-cause mortality rate of AFib among patients with HF in SSA.

Methods and analysis: The Preferred Reporting Items for Systematic Reviews and Meta-analyses for Protocols (PRISMA-P) 2015 statement was used to prepare this protocol. All eligible studies from database inception to 31 December 2017 in MEDLINE, Embase, Web of science and Africa-specific databases (AFROLIB, African Index Medicus and African Journals Online) will be included without language restrictions. The process of study screening, selection, data extraction and assessment of risk of bias will be conducted independently by two reviewers. Disagreements will be arbitrated by a third reviewer. Study-specific estimates will be pooled using a random-effect meta-analysis, and summary measures obtained will be presented in forest plots. The $\chi 2$ test on Cochrane's Q and the I^2 statistics will be used to assess and quantify heterogeneity, respectively. The Egger's test and funnel plots will be used to assess publication bias.

Ethics and dissemination: Since our review will be based on already published data, an ethical approval is not required. The findings of this review will be presented in conferences and peer-reviewed journals, and shared on social media such as Researchgate, Facebook, WhatsApp and Twitter.

Trial registration number: This protocol is registered with the International Prospective Register of systematic reviews (PROSPERO: http://www.crd.york.ac.uk/PROSPERO) database with the registration number: CRD42018087564.

Strengths and limitations of this study

1. This will be the first systematic review and meta-analysis to evaluate the prevalence and incidence, and the mortality rate of atrial fibrillation (AFib) among heart failure (HF) patients in sub-Saharan Africa (SSA).
2. Our largely sensitive search strategy is anticipated to capture the maximum number of studies on the subject in SSA.
3. Robust statistical methods will be used to summarise data on the prevalence and incidence, and mortality of AFib among HF patients in SSA.
4. Heterogeneity in study-specific estimates of the prevalence, incidence and mortality of AFib across studies is a possible limitation to the study.

Introduction

The rapid transition in disease epidemiology from communicable to chronic non-communicable diseases (NCDs) in sub-Saharan Africa (SSA) has been particularly linked to the increasing prevalence cardiovascular risk factors such as hypertension, diabetes, obesity and dyslipidemia, and poor dietary and sedentary lifestyles owing to the breeze of westernization and urbanization [1–3]. Cardiovascular disease (CVD) is the leading cause of death globally, and is set to overtake infectious diseases as the top killer in SSA in the next two decades [4].

Heart failure (HF) is a major public health threat in SSA. It is the leading cause of admission into cardiology units and is associated with longer duration of hospital stay, high rates of readmissions and mortality, and a huge economic burden [5,6]. On the other hand, atrial fibrillation (AFib) remains the commonest cardiac arrhythmia globally, and its prevalence in Africa is expected to rise due to increasing prevalence of risk factors of AFib such as rheumatic heart disease, hypertension, diabetes, obesity, cardiopathy and ageing population [1,7,8]. It is associated with a high risk of thromboembolic events, especially stroke, morbidity and mortality [8]. Patients with HF in SSA are particularly prone to AFib and its complications due to the significant contributions of hypertension, cardiomyopathy and rheumatic valvular disease in the development of HF in the region [5]. Atrial fibrillation is a major decompensating factor and predictor of mortality among HF patients in SSA [5], and elsewhere [9,10]. Atrial fibrillation in HF is associated with higher readmissions rates, longer hospital stay and mortality among patients with HF [9,10]. Meanwhile, an integration of anti-coagulants, and anti-arrhythmic drugs such as beta-blockers and digoxin in the treatment of HF in SSA remains unacceptably low [5]. This is aggravated by the unavailability of these drugs in the local pharmacies [11].

This systematic review and meta-analysis seeks to summarize data on the prevalence and incidence, and all-cause mortality rate of atrial fibrillation among adult patients with HF in SSA. The result of this study will go a long way to inform healthcare professionals and policymakers on the burden of AFib among HF patients in SSA so that adequate measures can be implemented to curb the morbidity and mortality associated with AFib among patients with HF in the region.

Objective

To evaluate the prevalence, incidence and mortality rates of atrial fibrillation among adults with heart failure residing in SSA.

Review questions

1. What is the prevalence of atrial fibrillation among patients with heart failure in SSA?
2. What is the incidence of atrial fibrillation among patients with heart failure in SSA?
3. What is the all-cause mortality rate among patients with heart failure and atrial fibrillation SSA?

Methods and analysis

Criteria for considering studies for the review

Inclusion criteria

1. Observational studies reporting on the prevalence (cross-sectional and cohort studies), incidence (cohort and randomized controlled trials) and all-cause mortality rates (cross-sectional, cohort and randomized controlled trials) of atrial fibrillation among heart failure patients in SSA.

2. Age limit: Participants must be at least 15 years of age.
3. For duplicate studies: We shall include only the most recent and/or comprehensive study with the largest sample.
4. Publication date: From database inception to December 31, 2017.

Exclusion criteria

We shall exclude

1. Letters to the editor, editorials, commentaries, review articles and case-series with fewer than 30 participants
2. Studies with incomplete data which could not be recovered even after a reasonable request from the corresponding author of the study.

Information sources

Search strategy for identifying relevant studies

MEDLINE, Embase, Web of science and Africa-specific databases (AFROLIB, African Index Medicus and African Journals Online) will be searched from the inception date of each database to December 31, 2017 for relevant abstracts with information of the prevalence, incidence and/or mortality rate of AFib among SSA patients with HF. Medical subject headings and key text words like “Atrial fibrillation” and “heart failure” will be used to build the search strategy the search. A validated search filter [12] will be used to increase the precision of our search. Table 1 depicts the main strategy for MEDLINE. This strategy will be adapted to suit other databases.

The full-texts of eligible abstracts will be retrieved and assessed for final inclusion in the review. Database searches will be supplemented by scrutinizing the reference lists of eligible articles and relevant reviews for additional studies. In case the full-text of an article cannot be retrieved online, the corresponding author will be contacted via their emails or other social platforms like Researchgate and a fortnightly reminder scheduled. If no response is received after eight reminder emails or before the end of the data extraction process, the study will be automatically excluded.

Study records

Data management

Titles and abstracts retrieved from database searches will initially be imported to the software EndNote V.7.4 for removal of duplicates. The unduplicated titles and abstracts will then be uploaded to Rayyan QCRI [13]; a mobile and web-based application that facilitates collaboration between authors involved in study screening and selection for final inclusion in a systematic review. The process of study selection will be guided by a tool developed a priori based on the eligibility criteria.

Study screening

Two reviewers (CMM and FLT) will independently screen the titles and abstracts retrieved from the searches. Discrepancies in the screening of abstracts will be resolved through discussion and consensus. If disagreement persists a third reviewer (VNA) will be consulted for arbitration. Two reviewers (CMM and FLT) will then download and independently screen the full-texts of

selected records for final inclusion. Discrepancies and disagreements will be handled as mentioned above.

Data items and extraction

Using pre-established data extraction sheets, two reviewers (CMM and SNP) will independently extract data depending on the outcomes of interest: prevalence, incidence and all-cause mortality rates of AFib among patients with HF in SSA. Generally, data will be extracted on: the surname of the last author and year of study publication; the country in which the study was conducted; the region (western, central, southern and eastern); study setting (Hospital- versus community-based); study design (cross-sectional, cohort, case-control or randomized controlled trials); sampling method (random, consecutive or exhaustive); data collection (prospective or retrospective); male proportion; mean or median age in years; age range in years; sample size. Additional data will be extracted on (1) The characteristics of heart failure such as the mean or median duration of heart failure in years, causes of heart failure (like hypertensive heart disease, cardiomyopathy, rheumatic heart disease or ischaemic heart disease), and severity of heart failure (according to the New York Heart Association classification and/or left ventricular ejection fraction on echocardiography); and (2) the characteristics of atrial fibrillation: mean or median duration since diagnosis in years, type of atrial fibrillation (paroxysmal, persistent or permanent) and proportion of participants on any anticoagulation therapy.

In addition to the aforementioned data items to be extracted, we shall extract data on: the number of AFib cases in patients with HF. To determine the incidence of AFib in HF patients, additional data will be extracted on the number of new cases of AFib among patients with HF. Finally, data will be extracted on the mean duration of follow up, and the number of deaths due to any cause

among HF patients with AFib in order to determine all-cause mortality among HF patients with AFib.

For multinational studies, data on the outcome of interest (prevalence, incidence and mortality rate of AFib in HF) will be disaggregated according to the countries in which the study was conducted. Otherwise, these studies will be presented as a single study and the countries where the study was conducted in will be highlighted. The extracted data will be cross-checked at least once by two authors (LNA and VNA) for consistency and obvious errors.

Assessment of methodological quality and risk of bias.

Two reviewers (CMM and SNP) will independently assess the included full-texts for bias. The risk of bias and quality of included studies reporting on prevalence and incidence measures will be assess using the risk of bias tool for prevalence studies proposed by Hoy *et al* [14], adapted for the purpose of this study, **supplementary file 1**. Also, the Quality In Prognosis Studies (QUIPS) tool (**supplementary file 2)** [15] will be used to evaluate the risk of bias or quality of studies reporting on the mortality rate among HF patients with AFib. Disagreements during this process will be arbitrated by a single reviewer (CD).

Data synthesis and analysis

The *'meta'* package of the R software will be used to analyze extracted data. Study-specific prevalence, incidence and mortality estimates will recalculated using crude numerators and denominators from the individual studies. Using the Freeman-Tukey single arc-sine transformation, the variance of study-specific estimates will be stabilized before pooling with the random effect meta-analysis model [16]. Heterogeneity across studies will be assessed and quantified using the Cochrane's Q and I-squared (I^2) statistics, respectively [17]. Low, medium

and substantial heterogeneity will be represented by I^2 values of 25%, 50% and 75% respectively [18]. A subgroup analysis using the following variables will performed in cases of substantial heterogeneity: Region (western, central, southern and eastern); study type (Hospital versus community-based); study design; study area (urban, rural or both); random sampling (yes versus no); data collection (prospective versus retrospective); gender (male versus female); age group (below versus at or above the median age); cause of heart failure (valvular versus non-valvular); severity of heart failure (NYHA stage I and II versus III and IV; and EF < 35% versus ≥ 35%); type of AFib (paroxysmal, persistent or permanent); and study quality.

Estimates of the prevalence, incidence and all-cause mortality rates will be pooled according to the SSA region and compared using the Q-test on analysis of variance. Publication bias will be assessed with the aid of a symmetry of forest plots and Egger's test [19]. A p-value below 10% on Egger's test will be considered statistically significant.

Presentation and reporting of results

This review will be published in accordance with the recommended of the PRISMA statement [20]. With the aid of a flow diagram the process of study screening, selection, final inclusion and reasons for study exclusion will be demonstrated. Where necessary, summary tables and forest plots will be used to display quantitative data. The risk of bias for all the included studies will be presented using narrative summaries and tables.

The prevalence and incidence of AFib among HF patients with HF and the mortality rate of HF patients with HF will be reported according to the SSA region (western, eastern, southern and central), cause of HF (valvular versus non-valvular), heart failure severity (NYHA stage I and II

versus III and IV; and EF < 35% versus ≥ 35%) and study type (hospital-based versus community-based).

Protocol amendments

We do not plan to modify the present protocol. However, any modification will be succinctly described in the final review.

Ethics and dissemination

Since the review is based on already published data, an ethical approval is not required. The findings of this review will be presented in conferences and peer-reviewed journals, and shared on social media such as ResearchGate, Facebook, WhatsApp and Twitter.

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Contributors: VNA conceived the study. VNA, LNA and JJN:designed the study protocol. VNA drafted the initial manuscript. LNA, FLT, CMM, SNP, CD and JJN critically revised the protocol for methodological and intellectual content. All authors read and approved the final version of the manuscript prior to submission. VNA is the guarantor of the review.

Competing interest: None.

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Data sharing statement

No additional data are available

Table 1: Search strategy for PubMed

Supplementary file 1: Adapted Hoy et al tool for risk of bias assessment of studies reporting on the prevalence and incidence of atrial fibrillation in patients with heart failure

Supplementary file 2: Quality In Prognosis Studies (QUIPS) tool for assessment of risk of bias among studies reporting on mortality in heart failure patients with atrial fibrillation

Table 1: Search strategy for PubMed

SN	Search items
1.	"Heart failure"[Mesh] OR "Cardiac failure"[tiab] OR "Cardiac insufficiency"[tiab] OR "heart failure" [tiab]
2.	"Atrial fibrillation" [Mesh] OR "Atrial fibrillation" [tiab]
3.	**#1 AND #2**
4.	benin/ or burkina faso/ or cape verde/ or cote d'ivoire/ or gambia/ or ghana/ or guinea/ or guinea-bissau/ or liberia/ or mali/ or mauritania/ or nigeria/ or senegal/ or sierra leone/ or togo/ or ((africa*adj2 west* or benin* or burkina fas* or cape verd* or cabo verd* or ivory coast or cote d'ivoire* or gambia* or ghana* or (guinea* not pig*) or bissau or liberia* or (mali not fowl) or malian or mauritania* or nigeria* or senegal* or sierra leon* or togo*).mp. or (Lagos or Accra or Abidjan or Dakar or Abobo or Abuja or Freetown or Ouagadougou or Conakry or Lome or Bamako or Cotonou or Kumasi or Monrovia or Ibadan or Kano or Port harcourt or Benin City or Porto Novo or Niamey or Yamoussoukro or Banjul or Timbuktu or Djenne or Abomeyu or Zaria or Tamale or Jos or Cape Coast or Maidugul or Aba or Gao or Calabar or Warri or Maiduguri or Bobo Dioulasso or Parakou or Djougou or Bohicon or Sekondi Takoradi or Sunyani or Obuasi or Teshie or Tema or Sikasso or Kalabankoro or Nouakchott or Dakhlet Nouadhibou or Benin City or Port Harcourt or Ilorin or Kaduna or Enugu or Ikorodu or Onitsha or Bauchi or Akure or Abeokuta or Sokoto or Bouake or Makeni or Kaduan or Sosgbo or Osogbo or Gombe or Ilesa or Badagry or makurdi or Sagamu or Iseyin or obbomosho or Awka or Ado Ekiti or Nsukka or Ikeja or Katsina or Okene or Lafia or Minna or Ondo city or Umuahia or Calabar or Yola or Pikine or Touba or Thies Nones or Saint Louis or Kolak or Ziguinch or (San Pedro not (Spain or Mexico or Argentina or California or United States or Italy)) or Bandama or Daloa or Owerri or Kandi or Ifi or Dakar or Ogbomosho or Divo or Korhogo)).ti,ab or Exp africa, central/ or ((africa adj2 central) or angola or cameroon* or chad.mp. or tchad.mp. or congo* or DRC or equatorial guinea* or gabon* or Sao Tome or Principe or Luanda or lobito or kuito or huambo or Malanje or Douala or Yaounde or Bamenda or Garoua of

Bafoussam or Nganoundere or Maroua or Kouosseri or Buena or Kumba or N'Djamena or Moundou or Bangui or Bimbo or Brazzaville or Point Noire or Kinshasa or Lubumbashi or Leopoldville or Elizabethville or Mbuji Mayi or Bakwanga or Bukavu or Costermansville or Kananga or Luluabourg or Kisangani or Stanleyville or Tshikapa or Koalwezi or Likasi or Jadotville or Goma or Kikwit or Uvira or Bunia or Mbandaka or Coquilhatville or Matadi or Butembo or Kabinda or Mwene Ditu or Isiro or Paulis or Boma or Kindu or Bata or Malabo or Libreville).ti,ab or Exp Africa, Eastern/ or ((east* adj2 africa*) or British Indian Ocean Territory or Burundi* or Comoros or Djibouti* or Eritrea* or Ethiopia* or Kenya* or Madagascar or Malawi or Mauritius or Mayotte or Mozambique or Reunion OR Rwanda* or Seychelles or Somalia* or Sudan* or Tanzania* or Uganda* or Zambia or Zimbabwe or Crozet Islands or Iles Crozet or Scattered Islands or Iles Eparses or Mwanza or Zanzibar or Eldoret or Morogoro or Hargeysa or Berbera or Nyeri or Mbeya or Machakos or Marka or Tabora or Iringa or Gondar or Meru or Geita or Musoma or Mtwara or Songea or Kigoma or Dese or Mek'ele or Bahir Dar or Jimma or Sinyanga or Korogwe or Nairobi or "Dar es Salaam" or Mombasa or Addis Ababa or Kampala or Kigali or Mogadishu or Dodomoa or Bujumbura or Nakuru or Anananarivo or Kisumu or Maputo or Asmara or Lusaka or Harare or Port Louis or Arusha or kitale or lilongwe or malindi or machakos or hargeisa or Bulawayo or Ruiru or Lamu or Kire Dawa or Kikuyu or naivasha or mwanza or tanga or nanyuki or voi or garissa or lodwar of kakamega or maralal or kitui or webuye or Axum or Nyahururu or Jinja or Kismayo or Namanga or Mumias or Moshi or Moroni or Lokichogio or Hola or Rwenzori Mountains or Lake Victoria or Puntland* or (Adiharush or Ali-Addeh or Alinjugur or Buramino or Dadaab or Dagahaley or Dollo Ado or Fugnido or Hagadera or Hilaweyn or Ifo or Kakuma or Kambioos or Kayaka II or Kobe or Kyangwali Nakivale or Nyarugusu or Wad Sherife or Bokolmanyo or Melkadida or Rwamanja) adj5 (camp or refug*)).ti,ab or angola/ or botswana/ or lesotho/ or malawi/ or mozambique/ or namibia/ or south africa/ or swaziland/ or zambia/ or zimbabwe/ or ((africa* adj2 south*) or angola* or botswana* or lesotho* or malawi* or mozambiq* or namibia* or swaziland or zambia* or zimbabwe or Zulu or Tsonga or Xhosa or Swazi or Ndebele or Tswana or Sotho or Shona people or BaLunda or Mbundu or Ovimbundu or Chaga or Sukuma or Pretoria or Cape Town or Johannesburg or Durban or Port Elizabeth or Bloemfontein or Windhoek or Maseru or Pietermaritz or (Kimberley not Australia) or Nespruit or Soweto or Polokwane or Limpopo or Rustenburg or Mahikeng or Oudtshroom or Stellenbosch or Paarl or Gaborone or Luanda or Cabinda or Huambo or Lubango or Kuit or Malanje or Lobito or Lilongwe or Blantyre or Mzuzu or Maputo or Matola or Beira or Nampula or Chimoio or Nacala or Quelimane or Lusaka or Kitwe or Ndola or Kabwe or Copperbelt Harare or Bulawayo or Chitungwiza or Mutare or Masvingo or Monashonaland or Manicaland).ti,ab.

5. **#3 AND #4**
6. Publication date limits: from database inception to 31 December 2017, with no language restrictions

Quality assessment checklist for prevalence studies (adapted from Hoy et al)

Name of author(s): Year of publication: Study title:		
Risk of bias items	**Risk of bias levels**	**Points scored**
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	**Yes** (**LOW RISK**): The study's target population was a close representation of the national population.	0
	No (**HIGH RISK**): The study's target population was clearly NOT representative of the national population.	1
2. Was the sampling frame a true or close representation of the target population?	**Yes** (**LOW RISK**): The sampling frame was a true or close representation of the target population.	0
	No (**HIGH RISK**): The sampling frame was NOT a true or close representation of the target population.	1
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	**Yes** (**LOW RISK**): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (**HIGH RISK**): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	**Yes** (**LOW RISK**): The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders	0
	No (**HIGH RISK**): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders	1
5. Were data collected directly from the subjects (as opposed to a proxy)?	**Yes** (**LOW RISK**): All data were collected directly from the subjects.	0
	No (**HIGH RISK**): In some instances, data were collected from a proxy.	1
6. Was an acceptable case definition used in the study?	**Yes** (**LOW RISK**): An acceptable case definition was used. **No** (**HIGH RISK**): An acceptable case definition was NOT used	0 1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes** (**LOW RISK**): The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	0
	No (**HIGH RISK**): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collection used for all subjects?	**Yes** (**LOW RISK**): The same mode of data collection was used for all subjects.	0
	No (**HIGH RISK**): The same mode of data collection was NOT used for all subjects.	1
9. Were the numerator(s) and denominato r(s) for the parameter of interest appropriate	**Yes** (**LOW RISK**): The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
	No (**HIGH RISK**): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10. Summary on the overall risk of study bias	**LOW RISK**	0-3
	MODERATE RISK	4-6
	HIGH RISK	7-9

Additional File 3. Adapted Quality In Prognosis Studies (QUIPS) list for scoring methodological quality of prognosis studies

Domains	Items for consideration	For each item	Quality
Study participation	a. Adequate participation in the study by eligible persons b. Description of the source population or population of interest c. Description of the baseline study sample d. Adequate description of the sampling frame and recruitment e. Adequate description of the period and place of recruitment f. Adequate description of inclusion and exclusion criteria	(+) = 3 (+/-) = 1.5 (-) = 0	High bias: 0-6 Moderate bias: 7-12 Low bias: 13-18
Study attrition	a. Adequate response rate for study participants b. Description of attempts to collect information on participants who dropped out c. Reasons for loss to follow-up are provided d. Adequate description of participants lost to follow-up e. There are no important differences between participants who completed the study and those who did not	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-8 Moderate bias: 9-16 Low bias: 17-25
PF measurement	a. A clear definition or description of the PF is provided b. Method of PF measurement is adequately valid and reliable c. Continuous variables are reported or appropriate cut points are used d. The method and setting of measurement of PF is the same for all study participants e. Adequate proportion of the study sample has complete data for the PF f. Appropriate methods of imputation are used for missing PF data	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-8 Moderate bias: 9-16 Low bias: 17-25
Outcome measurement	a. A clear definition of the outcome is provided b. Method of outcome measurement used is adequately valid and reliable c. The method and setting of outcome measurement is the same for all study participants	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-5 Moderate bias: 6-10 Low bias: 11-15
Study confounding	a. All important confounders are measured b. Clear definitions of the important confounders measured are provided c. Measurement of all important confounders is adequately valid and reliable d. The method and setting of confounding measurement are the same for all study participants e. Appropriate methods are used if imputation is used for missing confounder data f. Important potential confounders are accounted for in the study design g. Important potential confounders are accounted for in the analysis	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-12 Moderate bias: 13-24 Low bias: 25-35
Statistical analysis and reporting	a. Sufficient presentation of data to assess the adequacy of the analytic strategy b. Strategy for model building is appropriate and is based on a conceptual framework or model c. The selected statistical model is adequate for the design of the study d. There is no selective reporting of results	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-7 Moderate bias: 8-14 Low bias: 15-20

PF: prognostic factor

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	3
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	13
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	11
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
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	6-7
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	6, Table 1
Study records:			
Data	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7

management			
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)	7
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	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	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	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	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	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)	9-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

BMJ Open

Atrial fibrillation among adults with heart failure in sub-Saharan Africa; prevalence, incidence and all-cause mortality: a systematic review and meta-analysis protocol

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Secondary Subject Heading:	Epidemiology, Cardiovascular medicine
Keywords:	Heart failure < CARDIOLOGY, atrial fibrillation, Prevalence, Incidence, Mortality

Atrial fibrillation among adults with heart failure in sub-Saharan Africa; prevalence, incidence and all-cause mortality: a systematic review and meta-analysis protocol

Authors: Valirie Ndip Agbor[1,2*]; Leopold Ndemnge Aminde[3,4]; Frank-Leonel Tianyi[5]; Clarence Mvalo Mbanga[6]; Saint-Juste N. Petnga[7]; Chobufo Ditah[8]; Jean Jacques Noubiap[9]

Affiliations: [1] Ibal Sub-divisional Hospital, Oku, Northwest, Cameroon; [2] Department of Clinical Research, Health Education and Research Organization (HERO), Cameroon; [3] Non-communicable disease unit, Clinical Research Education, Networking and Consultancy (CRENC), Douala, Cameroon; [3] School of Public Health, Faculty of Medicine, University of Queensland, Brisbane, Australia; [4] Mayo-Darle sub-Divisional Hospital, Banyo, Adamawa Region, Cameroon; [5]Mankon sub-divisional Hospital, Bamenda, North-west Region, Cameroon; [6] Department of Public Health, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Yaoundé, Cameroon; [7] Doctors Without Borders-French Section (MSF-F), France; [8] Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa.

Email addresses: VNA: nvagbor@gmail.com; LNA: amindeln@gmail.com; FLT: tianyifrankleonel@gmail.com; CMM: mbangaclarence@gmail.com; SNP: p.ngass@gmail.com; CD: ditahdivine@yahoo.co.uk; JJN: noubiapjj@yahoo.fr

***Corresponding author:** Dr. Valirie Ndip Agbor, Ibal Sub-divisional Hospital, Oku, Northwest Region, Cameroon. Tel: 00 237 676546548, Email: nvagbor@gmail.com;

Keywords: Prevalence, incidence, mortality, atrial fibrillation, heart failure, sub-Saharan Africa

Abstract

Introduction: Heart failure (HF) remains a major non-communicable disease in sub-Saharan Africa (SSA) associated with high rates of readmission, mortality and loss of economic productivity as it affects mostly young and active adults. Atrial fibrillation (AFib) is a major determinant of mortality among patients with HF in SSA. Meanwhile, the use of anti-arrhythmic medications in the region remains unacceptably low. This review aims to evaluate the prevalence and incidence of AFib in adult patients with HF in SSA, and the all-cause mortality rate among patients with HF and AFib in the same population.

Methods and analysis: The Preferred Reporting Items for Systematic Reviews and Meta-analyses for Protocols (PRISMA-P) 2015 statement was used to prepare this protocol. All eligible studies from database inception to 31 August 2018 in MEDLINE, Embase, Google Scholar, Web of science and Africa-specific databases (AFROLIB, African Index Medicus and African Journals Online) will be included without language restrictions. The process of study screening, selection, data extraction and assessment of risk of bias will be conducted independently by two reviewers. Disagreements will be arbitrated by a third reviewer. Study-specific estimates will be pooled using a random-effect meta-analysis, and summary measures obtained will be presented in forest plots. The $\chi 2$ test on Cochrane's Q and the I^2 statistics will be used to assess and quantify heterogeneity, respectively. The Egger's test and funnel plots will be used to assess publication bias.

Ethics and dissemination: Since our review will be based on already published data, an ethical approval is not required. The findings of this review will be presented in conferences and peer-

reviewed journals, and shared on social media such as Researchgate, Facebook, WhatsApp and Twitter.

Trial registration number: This protocol is registered with the International Prospective Register of systematic reviews (PROSPERO: http://www.crd.york.ac.uk/PROSPERO) database with the registration number: CRD42018087564.

Strengths and limitations of this study

1. This will be the first systematic review and meta-analysis to evaluate the prevalence and incidence of atrial fibrillation (AFib) among heart failure (HF) patients in sub-Saharan Africa (SSA), and the mortality rate of HF patients with AFib in the same population.
2. Our largely sensitive search strategy is anticipated to capture the maximum number of studies on the subject in SSA.
3. Robust statistical methods will be used to summarise data on the selected primary outcomes.
4. Due to the possibility of missing patients with asymptomatic and brief episodes of AFib by individual studies, this review might underestimate the incidence and/or prevalence of AFib among African patients with HF. On the other hand, there is a probability of overestimating the prevalence of AFib in HF as cross-sectional studies do not permit to know which affection started first.
5. Heterogeneity in study-specific estimates of the prevalence, incidence and mortality of AFib across studies is a possible limitation to the study.

Introduction

The rapid transition in disease epidemiology from communicable to chronic non-communicable diseases (NCDs) in sub-Saharan Africa (SSA) has been particularly linked to the increasing prevalence cardiovascular risk factors such as hypertension, diabetes, obesity and dyslipidemia, and poor dietary and sedentary lifestyles owing to the breeze of westernization and urbanization [1–3]. Cardiovascular disease (CVD) is the leading cause of death globally, and is said to overtake infectious diseases as the top killer in SSA in the next two decades [4].

Heart failure (HF) is a major public health threat in SSA. It is the leading cause of admission into cardiology units and is associated with longer duration of hospital stay, high rates of readmissions and mortality, and a huge economic burden [5, 6]. On the other hand, atrial fibrillation (AFib) remains the commonest cardiac arrhythmia globally, and its prevalence in Africa is expected to rise due to increasing prevalence of risk factors such as rheumatic heart disease, hypertension, diabetes, obesity, cardiopathy and ageing population [1, 7, 8]. It is associated with a high risk of thromboembolic events, especially stroke, morbidity and mortality [8]. Patients with HF in SSA are particularly prone to AFib and its complications due to the significant contributions of hypertension, cardiomyopathy and rheumatic valvular disease in the development of HF in the region [5]. About 16 - 20.7% of HF patients in SSA are diagnosed with AFib [9–11]. Atrial fibrillation is a major decompensating factor and predictor of mortality among HF patients in SSA [5] and elsewhere [12, 13]. In fact, HF patients with AFib are 1.3 – 3.4 times at risk of death compared to their counterparts without AFib [6, 9]. Atrial fibrillation is

associated with over 25% of all-cause mortality among patients with HF in SSA [11]. Moreover, HF patients with AFib are at risk of higher readmissions rates, longer hospital stay and mortality compared to those without AFib [12, 13]. Meanwhile, the integration of anti-coagulants and anti-arrhythmic drugs such as beta-blockers and digoxin in the treatment of HF in SSA remains unacceptably low [5]. This is aggravated by the unavailability of these drugs in the local pharmacies [14]. In addition to being a complication of HF, AFib can be the aetiology of HF through the development of atrial cardiomyopathy [15–17].

This systematic review and meta-analysis will focus on atrial fibrillation as a complication of heart failure. It therefore seeks to summarize data on the prevalence and incidence of AFib in adults with HF in SSA, and all-cause mortality of patients with HF and AFib in the same population. The result of this study will go a long way to inform healthcare professionals and policymakers on the burden of AFib among HF patients in SSA so that adequate measures can be implemented to curb the morbidity and mortality associated with AFib among patients with HF in the region.

Objective

To estimate the prevalence and incidence of atrial fibrillation among adult patients with heart failure in SSA, and the mortality rate of patients with heart failure and atrial fibrillation in the same population.

Review questions

1. What is the prevalence of atrial fibrillation among patients with heart failure in SSA?
2. What is the incidence of atrial fibrillation among patients with heart failure in SSA?

3. What is the proportion of all-cause mortality rate among heart failure patients with atrial fibrillation in SSA?

Methods and analysis

Criteria for considering studies for the review

Inclusion criteria

1. Observational studies reporting on the prevalence (cross-sectional and cohort studies) and/or incidence (cohort and randomized controlled trials) of atrial fibrillation in patients with heart failure, and/or all-cause mortality rates (cross-sectional, cohort and randomized controlled trials) among patients with heart failure and atrial fibrillation in SSA.
2. Age limit: Participants must be at least 15 years of age.
3. For duplicate studies: We shall include only the most recent and/or comprehensive study with the largest sample.
4. Publication date: From database inception to December 31, 2017.

Exclusion criteria

We shall exclude

1. Letters to the editor, editorials, commentaries, review articles and case-series with fewer than 30 participants.

2. Studies conducted in participants with an initial diagnosis of atrial fibrillation without heart failure.
3. Studies with incomplete data which could not be recovered even after a reasonable request from the corresponding author of the study.

Information sources

Search strategy for identifying relevant studies

MEDLINE, Embase, Google Scholar, Web of science and Africa-specific databases (AFROLIB, African Index Medicus and African Journals Online) will be searched from the inception date of each database to August 31, 2018 for relevant abstracts with information on the prevalence and/or incidence of AFib in HF, and/or mortality rate among HF patients with AFib in SSA. Medical subject headings and key text words like "atrial fibrillation" and "heart failure" will be used to build the search strategy the search. A validated search filter [18] will be used to increase the geographic precision of our search. Table 1 depicts the main strategy for MEDLINE. This strategy will be adapted to suit other databases.

The full-texts of eligible abstracts will be retrieved and assessed for final inclusion in the review. Database searches will be supplemented by scrutinizing the reference lists of eligible articles and relevant reviews for additional studies. In case the full-text of an article cannot be retrieved online, the corresponding author will be contacted via their emails or other social platforms like Researchgate and a fortnightly reminder scheduled. If no response is received after eight reminder emails or before the end of the data extraction process, the study will be automatically excluded.

Study records

Data management

Titles and abstracts retrieved from database searches will initially be imported to the software EndNote V.7.4 for removal of duplicates. The unduplicated titles and abstracts will then be uploaded to Rayyan QCRI [19]; a mobile and web-based application that facilitates collaboration between authors involved in study screening and selection for final inclusion in a systematic review. The process of study selection will be guided by a tool developed a priori based on the eligibility criteria.

Study screening

Two reviewers (CMM and FLT) will independently screen the titles and abstracts retrieved from the searches. Discrepancies in the screening of abstracts will be resolved through discussion and consensus. If disagreement persists a third reviewer (VNA) will be consulted for arbitration. Two reviewers (CMM and FLT) will then download and independently screen the full-texts of selected records for final inclusion. Discrepancies and disagreements will be handled as mentioned above.

Data items and extraction

Using a pre-established Google data abstraction form, two reviewers (CMM and SNP) will independently extract data (online) depending on the outcomes of interest: prevalence, incidence and all-cause mortality rates of AFib among patients with HF in SSA. Generally, data will be extracted on: the surname of the last author and year of study publication; the country in which

the study was conducted; the region (western, central, southern and eastern); study setting (Hospital- versus community-based); study design (cross-sectional, cohort, case-control or randomized controlled trials); sampling method (random, consecutive or exhaustive); data collection (prospective or retrospective); male proportion; mean or median age in years; age range in years; proportion of anticoagulant use; proportion of beta-blocker use; and sample size. Additional data will be extracted on (1) The characteristics of heart failure such as the mean or median duration of heart failure in years, causes of heart failure (like hypertensive heart disease, cardiomyopathy, rheumatic heart disease or ischaemic heart disease), and severity of heart failure (according to the New York Heart Association classification and/or left ventricular ejection fraction on echocardiography); and (2) the characteristics of atrial fibrillation: mean or median duration since diagnosis in years, type of atrial fibrillation (paroxysmal, persistent or permanent) and proportion of participants on any anticoagulation therapy.

In addition to the aforementioned data items to be extracted, we shall extract data on: the number of AFib cases in patients with HF. To determine the incidence of AFib in HF patients, additional data will be extracted on the number of new cases of AFib among patients with HF. Finally, data will be extracted on the mean duration of follow up, the number of death due to any cause among patients with HF, and the number of deaths due to any cause among HF patients with AFib in order to determine proportion of all-cause mortality among HF patients with AFib.

For multinational studies, data on the outcome of interest will be disaggregated according to the countries in which the study was conducted. Otherwise, these studies will be presented as a single study and the countries where the study was conducted in will be highlighted. The extracted data will be cross-checked at least once by two authors (LNA and VNA) for consistency and obvious errors.

A duplicate of the online data abstraction form will be created for both authors responsible for data extraction (CMM and SNP), while the consistency of the extracted data will be monitored online by a third author (LNA) who will conduct the statistical analysis. Disagreements among authors will be resolved through consensus.

Assessment of methodological quality and risk of bias.

Two reviewers (CMM and SNP) will independently assess the included full-texts for bias. The risk of bias and quality of included studies reporting on prevalence and incidence measures will be assess using the risk of bias tool for prevalence studies proposed by Hoy *et al* [20], adapted for the purpose of this study, **supplementary file 1**. Also, the Quality In Prognosis Studies (QUIPS) tool (**supplementary file 2)** [21] will be used to evaluate the risk of bias or quality of studies reporting on the mortality rate among HF patients with AFib. Disagreements during this process will be arbitrated by a single reviewer (CD).

Data synthesis and analysis

The author, LNA, will conduct the statistical analysis. The *'meta'* package of the statistical software R (version 3.3.3, The R Foundation for statistical computing, Vienna, Austria) will be used to analyze the extracted data. Study-specific prevalence, incidence and mortality estimates will be recalculated using crude numerators and denominators from the individual studies. Using the Freeman-Tukey single arc-sine transformation, the variance of study-specific estimates will be stabilized before pooling with the random effect meta-analysis model [22]. Heterogeneity across studies will be assessed and quantified using the Cochrane's Q and I-squared (I^2) statistics, respectively [23]. Low, medium and substantial heterogeneity will be represented by I^2 values of 25%, 50% and 75% respectively [24]. A subgroup analysis using the following

variables will performed in cases of substantial heterogeneity: region (western, central, southern and eastern); study type (Hospital versus community-based); study design; study area (urban, rural or both); random sampling (yes versus no); data collection (prospective versus retrospective); gender (male versus female); age group (below versus at or above the median age); cause of heart failure (valvular versus non-valvular); severity of heart failure (NYHA stage I and II versus III and IV; and EF < 35% versus ≥ 35%); type of AFib (paroxysmal, persistent or permanent); proportion of anticoagulants and beta-blocker use (as continuous variables); and study quality.

Estimates of the prevalence, incidence and all-cause mortality rates will be pooled according to the SSA region and compared using the Q-test on analysis of variance. Publication bias will be assessed with the aid of a symmetry of forest plots and Egger's test [25]. A p-value below 10% on Egger's test will be considered statistically significant.

Presentation and reporting of results

This review will be published in accordance with the PRISMA statement [26]. With the aid of a flow diagram, the process of study screening, selection, final inclusion and reasons for study exclusion will be demonstrated. Where necessary, summary tables and forest plots will be used to display quantitative data. The risk of bias for all the included studies will be presented using narrative summaries and tables.

The prevalence and incidence of AFib among HF patients, and the mortality rate of HF patients with AFib will be reported according to the SSA region (western, eastern, southern and central), cause of HF (valvular versus non-valvular), heart failure severity (NYHA stage I and II versus III and IV; and EF < 35% versus ≥ 35%) and study type (hospital-based versus community-based).

Protocol amendments

We do not plan to modify the present protocol. However, any modification will be succinctly described in the final review.

Patient and public involvement

Patients and/or the public were not directly involved in this study.

Ethics and dissemination

Since the review is based on already published data, an ethical approval is not required. The findings of this review will be presented in conferences and peer-reviewed journals, and shared on social media such as ResearchGate, Facebook, WhatsApp and Twitter.

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Contributors: VNA conceived the study. VNA, LNA and JJN: designed the study protocol. VNA drafted the initial manuscript. LNA, FLT, CMM, SNP, CD and JJN critically revised the protocol for methodological and intellectual content. All authors read and approved the final version of the manuscript prior to submission. VNA is the guarantor of the review.

Competing interest: None.

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Data sharing statement

No additional data are available

Table 1: Search strategy for PubMed

Supplementary File 1: Quality assessment checklist for prevalence studies (adapted from Hoy *et al*)

Supplementary file 2: Adapted Quality In Prognosis Studies (QUIPS) list for scoring methodological quality of prognosis studies

Table 1: Search strategy for PubMed

SN	Search items
1.	"Heart failure"[Mesh] OR "Cardiac failure"[tiab] OR "Cardiac insufficiency" [tiab] OR "heart failure" [tiab]
2.	"Atrial fibrillation" [Mesh] OR "Atrial fibrillation" [tiab]
3.	**#1 AND #2**
4.	benin/ or burkina faso/ or cape verde/ or cote d'ivoire/ or gambia/ or ghana/ or guinea/ or guinea-bissau/ or liberia/ or mali/ or mauritania/ or nigeria/ or senegal/ or sierra leone/ or togo/ or ((africa*adj2 west* or benin* or burkina fas* or cape verd* or cabo verd* or ivory coast or cote d'ivoire* or gambia* or ghana* or (guinea* not pig*) or bissau or liberia* or (mali not fowl) or malian or mauritania* or nigeria* or senegal* or sierra leon* or togo*).mp. or (Lagos or Accra or Abidjan or Dakar or Abobo or Abuja or Freetown or Ouagadougou or Conakry or Lome or Bamako or Cotonou or Kumasi or Monrovia or Ibadan or Kano or Port harcourt or Benin City or Porto Novo or Niamey or Yamoussoukro or Banjul or Timbuktu or Djenne or Abomeyu or Zaria or Tamale or Jos or Cape Coast or Maidugul or Aba or Gao or Calabar or Warri or Maiduguri or Bobo Dioulasso or Parakou or Djougou or Bohicon or Sekondi Takoradi or Sunyani or Obuasi or Teshie or Tema or Sikasso or Kalabankoro or Nouakchott or Dakhlet Nouadhibou or Benin City or Port Harcourt or Ilorin or Kaduna or Enugu or Ikorodu or Onitsha or Bauchi or Akure or Abeokuta or Sokoto or Bouake or Makeni or Kaduan or Sosgbo or Osogbo or Gombe or Ilesa or Badagry or makurdi or Sagamu or Iseyin or obbomosho or Awka or Ado Ekiti or Nsukka or Ikeja or Katsina or Okene or Lafia or Minna or Ondo city or Umuahia or Calabar or Yola or Pikine or Touba or Thies Nones or Saint Louis or Kolak or Ziguinch or (San Pedro not (Spain or Mexico or Argentina or California or United States or Italy)) or Bandama or Daloa or Owerri or Kandi or Ifi or

Dakar or Ogbomosho or Divo or Korhogo)).ti,ab or Exp africa, central/ or ((africa adj2 central) or angola or cameroon* or chad.mp. or tchad.mp. or congo* or DRC or equatorial guinea* or gabon* or Sao Tome or Principe or Luanda or lobito or kuito or huambo or Malanje or Douala or Yaounde or Bamenda or Garoua of Bafoussam or Nganoundere or Maroua or Kouosseri or Buena or Kumba or N'Djamena or Moundou or Bangui or Bimbo or Brazzaville or Point Noire or Kinshasa or Lubumbashi or Leopoldville or Elizabethville or Mbuji Mayi or Bakwanga or Bukavu or Costermansville or Kananga or Luluabourg or Kisangani or Stanleyville or Tshikapa or Koalwezi or Likasi or Jadotville or Goma or Kikwit or Uvira or Bunia or Mbandaka or Coquilhatville or Matadi or Butembo or Kabinda or Mwene Ditu or Isiro or Paulis or Boma or Kindu or Bata or Malabo or Libreville).ti,ab or Exp Africa, Eastern/ or ((east* adj2 africa*) or British Indian Ocean Territory or Burundi* or Comoros or Djibouti* or Eritrea* or Ethiopia* or Kenya* or Madagascar or Malawi or Mauritius or Mayotte or Mozambique or Reunion OR Rwanda* or Seychelles or Somalia* or Sudan* or Tanzania* or Uganda* or Zambia or Zimbabwe or Crozet Islands or Iles Crozet or Scattered Islands or Iles Eparses or Mwanza or Zanzibar or Eldoret or Morogoro or Hargeysa or Berbera or Nyeri or Mbeya or Machakos or Marka or Tabora or Iringa or Gondar or Meru or Geita or Musoma or Mtwara or Songea or Kigoma or Dese or Mek'ele or Bahir Dar or Jimma or Sinyanga or Korogwe or Nairobi or "Dar es Salaam" or Mombasa or Addis Ababa or Kampala or Kigali or Mogadishu or Dodomoa or Bujumbura or Nakuru or Anananarivo or Kisumu or Maputo or Asmara or Lusaka or Harare or Port Louis or Arusha or kitale or lilongwe or malindi or machakos or hargeisa or Bulawayo or Ruiru or Lamu or Kire Dawa or Kikuyu or naivasha or mwanza or tanga or nanyuki or voi or garissa or lodwar of kakamega or maralal or kitui or webuye or Axum or Nyahururu or Jinja or Kismayo or Namanga or Mumias or Moshi or Moroni or Lokichogio or Hola or Rwenzori Mountains or Lake Victoria or Puntland* or (Adiharush or Ali-Addeh or Alinjugur or Buramino or Dadaab or Dagahaley or Dollo Ado or Fugnido or Hagadera or Hilaweyn or Ifo or Kakuma or Kambioos or Kayaka II or Kobe or Kyangwali Nakivale or Nyarugusu or Wad Sherife or Bokolmanyo or Melkadida or Rwamanja) adj5 (camp or refug*)).ti,ab or angola/ or botswana/ or lesotho/ or malawi/ or mozambique/ or namibia/ or south africa/ or swaziland/ or zambia/ or zimbabwe/ or ((africa* adj2 south*) or angola* or botswana* or lesotho* or malawi* or mozambiq* or namibia* or swaziland or zambia* or zimbabwe or Zulu or Tsonga or Xhosa or Swazi or Ndebele or Tswana or Sotho or Shona people or BaLunda or Mbundu or Ovimbundu or Chaga or Sukuma or Pretoria or Cape Town or Johannesburg or Durban or Port Elizabeth or Bloemfontein or Windhoek or Maseru or Pietermaritz or (Kimberley not Australia) or Nespruit or Soweto or Polokwane or Limpopo or Rustenburg or Mahikeng or Oudtshroom or Stellenbosch or Paarl or Gaborone or Luanda or Cabinda or Huambo or Lubango or Kuit or Malanje or Lobito or Lilongwe or Blantyre or Mzuzu or Maputo or Matola or Beira or Nampula or Chimoio or Nacala or Quelimane or Lusaka or Kitwe or Ndola or Kabwe or Copperbelt Harare or Bulawayo or Chitungwiza or Mutare or Masvingo or Monashonaland or Manicaland).ti,ab.

5. **#3 AND #4**

6. Publication date limits: from database inception to 31 August 2018, with no language restrictions

Supplementary File 1: Quality assessment checklist for prevalence studies (adapted from Hoy et al)

Name of author(s):

Year of publication:

Study title:

Risk of bias items	Risk of bias levels	Points scored
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	**Yes** (**LOW RISK**): The study's target population was a close representation of the national population.	0
	No (**HIGH RISK**): The study's target population was clearly NOT representative of the national population.	1
2. Was the sampling frame a true or close representation of the target population?	**Yes** (**LOW RISK**): The sampling frame was a true or close representation of the target population.	0
	No (**HIGH RISK**): The sampling frame was NOT a true or close representation of the target population.	1
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	**Yes** (**LOW RISK**): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (**HIGH RISK**): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	**Yes** (**LOW RISK**): The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders	0
	No (**HIGH RISK**): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders	1
5. Were data collected directly from the subjects (as opposed to a proxy)?	**Yes** (**LOW RISK**): All data were collected directly from the subjects.	0
	No (**HIGH RISK**): In some instances, data were collected from a proxy.	1
6. Was an acceptable case definition used in the study?	**Yes** (**LOW RISK**): An acceptable case definition was used.	0
	No (**HIGH RISK**): An acceptable case definition was NOT used	1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes** (**LOW RISK**): The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	0
	No (**HIGH RISK**): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collection used for all subjects?	**Yes** (**LOW RISK**): The same mode of data collection was used for all subjects.	0
	No (**HIGH RISK**): The same mode of data collection was NOT used for all subjects.	1
9. Were the numerator(s) and denominator(s) for the parameter of interest appropriate	**Yes** (**LOW RISK**): The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
	No (**HIGH RISK**): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10. Summary on the overall risk of study bias	**LOW RISK**	0-3
	MODERATE RISK	4-6
	HIGH RISK	7-9

Supplementary File 2: Adapted Quality In Prognosis Studies (QUIPS) list for scoring methodological quality of prognosis studies

Domains	Items for consideration	For each item	Quality
Study participation	a. Adequate participation in the study by eligible persons b. Description of the source population or population of interest c. Description of the baseline study sample d. Adequate description of the sampling frame and recruitment e. Adequate description of the period and place of recruitment f. Adequate description of inclusion and exclusion criteria	(+) = 3 (+/-) = 1.5 (-) = 0	High bias: 0-6 Moderate bias: 7-12 Low bias: 13-18
Study attrition	a. Adequate response rate for study participants b. Description of attempts to collect information on participants who dropped out c. Reasons for loss to follow-up are provided d. Adequate description of participants lost to follow-up e. There are no important differences between participants who completed the study and those who did not	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-8 Moderate bias: 9-16 Low bias: 17-25
PF measurement	a. A clear definition or description of the PF is provided b. Method of PF measurement is adequately valid and reliable c. Continuous variables are reported or appropriate cut points are used d. The method and setting of measurement of PF is the same for all study participants e. Adequate proportion of the study sample has complete data for the PF f. Appropriate methods of imputation are used for missing PF data	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-8 Moderate bias: 9-16 Low bias: 17-25
Outcome measurement	a. A clear definition of the outcome is provided b. Method of outcome measurement used is adequately valid and reliable c. The method and setting of outcome measurement is the same for all study participants	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-5 Moderate bias: 6-10 Low bias: 11-15
Study confounding	a. All important confounders are measured b. Clear definitions of the important confounders measured are provided c. Measurement of all important confounders is adequately valid and reliable d. The method and setting of confounding measurement are the same for all study participants e. Appropriate methods are used if imputation is used for missing confounder data f. Important potential confounders are accounted for in the study design g. Important potential confounders are accounted for in the analysis	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-12 Moderate bias: 13-24 Low bias: 25-35
Statistical analysis and reporting	a. Sufficient presentation of data to assess the adequacy of the analytic strategy b. Strategy for model building is appropriate and is based on a conceptual framework or model c. The selected statistical model is adequate for the design of the study d. There is no selective reporting of results	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-7 Moderate bias: 8-14 Low bias: 15-20

PF: prognostic factor

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	3
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	13
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	11
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
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	6-7
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	6, Table 1
Study records:			
Data	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7

management			
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)	7
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	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	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	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	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	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)	9-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

BMJ Open

Atrial fibrillation among adults with heart failure in sub-Saharan Africa; prevalence, incidence and all-cause mortality: a systematic review and meta-analysis protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022320.R2
Article Type:	Protocol
Date Submitted by the Author:	26-Nov-2018
Complete List of Authors:	Agbor, Ndip; Ibal sub-Divisional Hospital, General practice Aminde, Leopold; Clinical Research Education, Networking & Consultancy (CRENC), Douala, Frank Leonel, Tianyi Tianyi; Mayo Darle sub-Divisional Hospital, Mbanga, Clarence; Mankon Sub-divisional Hospital Petnga, Saint Just; Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Public Health Ditah, chobufo Noubiap, Jean Jacques; Edea Regional Hospital, Internal Medicine Unit
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Cardiovascular medicine
Keywords:	Heart failure < CARDIOLOGY, atrial fibrillation, Prevalence, Incidence, Mortality

Atrial fibrillation among adults with heart failure in sub-Saharan Africa; prevalence, incidence and all-cause mortality: a systematic review and meta-analysis protocol

Authors: Valirie Ndip Agbor[1,2*]; Leopold Ndemnge Aminde[3,4]; Frank-Leonel Tianyi[5]; Clarence Mvalo Mbanga[6]; Saint Just N. Petnga[7]; Chobufo Ditah[8]; Jean Jacques Noubiap[9]

Affiliations: [1] Ibal Sub-divisional Hospital, Oku, Northwest, Cameroon; [2] Department of Clinical Research, Health Education and Research Organization (HERO), Cameroon; [3] Non-communicable disease unit, Clinical Research Education, Networking and Consultancy (CRENC), Douala, Cameroon; [3] School of Public Health, Faculty of Medicine, University of Queensland, Brisbane, Australia; [4] Mayo-Darle sub-Divisional Hospital, Banyo, Adamawa Region, Cameroon; [5]Mankon sub-divisional Hospital, Bamenda, North-west Region, Cameroon; [6] Department of Public Health, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Yaoundé, Cameroon; [7] Doctors Without Borders-French Section (MSF-F), France; [8] Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa.

Email addresses: VNA: nvagbor@gmail.com; LNA: amindeln@gmail.com; FLT: tianyifrankleonel@gmail.com; CMM: mbangaclarence@gmail.com; SNP: p.ngass@gmail.com; CD: ditahdivine@yahoo.co.uk; JJN: noubiapjj@yahoo.fr

***Corresponding author:** Dr. Valirie Ndip Agbor, Ibal Sub-divisional Hospital, Oku, Northwest Region, Cameroon. Tel: 00 237 676546548, Email: nvagbor@gmail.com;

Keywords: Prevalence, incidence, mortality, atrial fibrillation, heart failure, sub-Saharan Africa

Abstract

Introduction: Heart failure (HF) remains a major non-communicable disease in sub-Saharan Africa (SSA) associated with high rates of readmission, mortality and loss of economic productivity as it affects mostly young and active adults. Atrial fibrillation (AFib) is a major determinant of mortality among patients with HF in SSA. Meanwhile, the use of anti-arrhythmic medications in the region remains unacceptably low. This review aims to evaluate the prevalence and incidence of AFib in adult patients with HF in SSA, and the all-cause mortality rate among patients with HF and AFib.

Methods and analysis: The Preferred Reporting Items for Systematic Reviews and Meta-analyses for Protocols (PRISMA-P) 2015 statement was used to prepare this protocol. All eligible studies from database inception to 31 August 2018 in MEDLINE, Embase, Google Scholar, Web of science and Africa-specific databases (AFROLIB, African Index Medicus and African Journals Online) will be included without language restrictions. The process of study screening, selection, data extraction and assessment of risk of bias will be conducted independently by two reviewers. Disagreements will be arbitrated by a third reviewer. Study-specific estimates will be pooled using a random-effect meta-analysis, and summary measures obtained will be presented in forest plots. The $\chi 2$ test on Cochrane's Q and the I^2 statistics will be used to assess and quantify heterogeneity, respectively. The Egger's test and funnel plots will be used to assess publication bias.

Ethics and dissemination: Since our review will be based on already published data, an ethical approval is not required. The findings of this review will be presented in conferences and peer-reviewed journals, and shared on social media such as Researchgate, Facebook, WhatsApp and Twitter.

Trial registration number: This protocol is registered with the International Prospective Register of systematic reviews (PROSPERO: http://www.crd.york.ac.uk/PROSPERO) database with the registration number: CRD42018087564.

Strengths and limitations of this study

1. This will be the first systematic review and meta-analysis to evaluate the prevalence and incidence of atrial fibrillation (AFib) among heart failure (HF) patients in sub-Saharan Africa (SSA), and the mortality rate of HF patients with AFib in the same population.
2. Our largely sensitive search strategy is anticipated to capture the maximum number of studies on the subject in SSA.
3. Robust statistical methods will be used to summarise data on the selected primary outcomes.
4. Due to the possibility of missing patients with asymptomatic and brief episodes of AFib by individual studies, this review might underestimate the incidence and/or prevalence of AFib among African patients with HF. On the other hand, there is a probability of overestimating the prevalence of AFib in HF as cross-sectional studies do not permit to know which pathology (AFib or HF) started first.
5. Heterogeneity in study-specific estimates of the prevalence, incidence and mortality of AFib across studies is a possible limitation to the study.

Introduction

The rapid transition in disease epidemiology from communicable to chronic non-communicable diseases (NCDs) in sub-Saharan Africa (SSA) has been particularly linked to the increasing prevalence cardiovascular risk factors such as hypertension, diabetes, obesity and dyslipidemia, and poor dietary and sedentary lifestyles owing to the breeze of westernization and urbanization [1–3]. Cardiovascular disease (CVD) is the leading cause of death globally, and is said to overtake infectious diseases as the top killer in SSA in the next two decades [4].

Heart failure (HF) is a major public health threat in SSA. It is the leading cause of admission into cardiology units and is associated with longer duration of hospital stay, high rates of readmissions and mortality, and a huge economic burden [5, 6]. On the other hand, atrial fibrillation (AFib) remains the commonest cardiac arrhythmia globally, and its prevalence in Africa is expected to rise due to increasing prevalence of risk factors such as rheumatic heart disease, hypertension, diabetes, obesity, cardiopathy and ageing population [1, 7, 8]. It is associated with a high risk of thromboembolic events, especially stroke, morbidity and mortality [8]. About 16 - 20.7% of HF patients in SSA are diagnosed with AFib [9–11]. Patients with HF in SSA are particularly prone to AFib and its complications due to the significant contributions of hypertension, cardiomyopathy and rheumatic valvular disease in the development of HF in the region [5]. In addition to being a complication of HF, AFib can be the aetiology of HF through the development of atrial cardiomyopathy [12–14]. Atrial fibrillation is a major decompensating factor and predictor of mortality among HF patients in SSA [5] and elsewhere [15, 16]. In fact, HF patients with AFib are 1.3 – 3.4 times at risk of death compared to their counterparts without AFib [6, 9]. Atrial fibrillation is associated with over 25% of all-cause mortality among patients with HF in SSA [11]. Moreover, HF patients with AFib are at risk of higher readmissions rates, longer hospital stay and mortality

compared to those without AFib [15, 16]. Meanwhile, the integration of anti-coagulants and anti-arrhythmic drugs such as beta-blockers and digoxin in the treatment of HF in SSA remains unacceptably low [5]. This is aggravated by the unavailability of these drugs in the local pharmacies [17].

This systematic review and meta-analysis will focus on atrial fibrillation as a complication of heart failure. It therefore seeks to summarize data on the prevalence and incidence of AFib in adults with HF in SSA, and all-cause mortality of patients with HF and AFib in the same population. The result of this study will go a long way to inform healthcare professionals and policymakers on the burden of AFib among HF patients in SSA so that adequate measures can be implemented to curb the morbidity and mortality associated with AFib among patients with HF in the region.

Objective

To estimate the prevalence and incidence of atrial fibrillation among adult patients with heart failure in SSA, and the mortality rate of patients with heart failure and atrial fibrillation in the same population.

Review questions

1. What is the prevalence of atrial fibrillation among patients with heart failure in SSA?
2. What is the incidence of atrial fibrillation among patients with heart failure in SSA?
3. What is the proportion of all-cause mortality rate among heart failure patients with atrial fibrillation in SSA?

Methods and analysis

Criteria for considering studies for the review

Inclusion criteria

1. Observational studies reporting on the prevalence (cross-sectional and cohort studies) and/or incidence (cohort and randomized controlled trials) of atrial fibrillation in patients with heart failure, and/or all-cause mortality rates (cross-sectional, cohort and randomized controlled trials) among patients with heart failure and atrial fibrillation in SSA.
2. Age limit: Participants must be at least 15 years of age.
3. For duplicate studies: We shall include only the most recent and/or comprehensive study with the largest sample.
4. Publication date: From database inception to December 31, 2017.

Exclusion criteria

We shall exclude

1. Letters to the editor, editorials, commentaries, review articles and case-series with fewer than 30 participants.
2. Studies conducted in participants with an initial diagnosis of atrial fibrillation without heart failure.
3. Studies with incomplete data which could not be recovered even after a reasonable request from the corresponding author of the study.

Information sources

Search strategy for identifying relevant studies

MEDLINE, Embase, Google Scholar, Web of science and Africa-specific databases (AFROLIB, African Index Medicus and African Journals Online) will be searched from the inception date of each database to August 31, 2018 for relevant abstracts with information on the prevalence and/or incidence of AFib in HF, and/or mortality rate among HF patients with AFib in SSA. Medical subject headings and key text words like "atrial fibrillation" and "heart failure" will be used to build the search strategy the search. A validated search filter [18] will be used to increase the geographic precision of our search. Table 1 depicts the main strategy for MEDLINE. This strategy will be adapted to suit other databases.

The full-texts of eligible abstracts will be retrieved and assessed for final inclusion in the review. Database searches will be supplemented by scrutinizing the reference lists of eligible articles and relevant reviews for additional studies. In case the full-text of an article cannot be retrieved online, the corresponding author will be contacted via their emails or other social platforms like Researchgate and a fortnightly reminder scheduled. If no response is received after eight reminder emails or before the end of the data extraction process, the study will be automatically excluded.

Study records

Data management

Titles and abstracts retrieved from database searches will initially be imported to the software EndNote V.7.4 for removal of duplicates. The unduplicated titles and abstracts will then be uploaded to Rayyan QCRI [19]; a mobile and web-based application that facilitates collaboration between authors involved in study screening and selection for final inclusion in a systematic

review. The process of study selection will be guided by a tool developed a priori based on the eligibility criteria.

Study screening

Two reviewers (CMM and FLT) will independently screen the titles and abstracts retrieved from the searches. Discrepancies in the screening of abstracts will be resolved through discussion and consensus. If disagreement persists a third reviewer (VNA) will be consulted for arbitration. Two reviewers (CMM and FLT) will then download and independently screen the full-texts of selected records for final inclusion. Discrepancies and disagreements will be handled as mentioned above.

Data items and extraction

Using a pre-established Google data abstraction form, two reviewers (CMM and SNP) will independently extract data (online) depending on the outcomes of interest: prevalence, incidence and all-cause mortality rates of AFib among patients with HF in SSA. Generally, data will be extracted on: the surname of the last author and year of study publication; the country in which the study was conducted; the region (western, central, southern and eastern); study setting (Hospital- versus community-based); study design (cross-sectional, cohort, case-control or randomized controlled trials); sampling method (random, consecutive or exhaustive); data collection (prospective or retrospective); male proportion; mean or median age in years; age range in years; proportion of anticoagulant use; proportion of beta-blocker use; and sample size. Additional data will be extracted on (1) The characteristics of heart failure such as the mean or median duration of heart failure in years, causes of heart failure (like hypertensive heart disease, cardiomyopathy, rheumatic heart disease or ischaemic heart disease), and severity of heart failure (according to the New York Heart Association classification and/or left ventricular ejection fraction on

echocardiography); and (2) the characteristics of atrial fibrillation: mean or median duration since diagnosis in years, type of atrial fibrillation (paroxysmal, persistent or permanent) and proportion of participants on any anticoagulation therapy.

In addition to the aforementioned data items to be extracted, we shall extract data on: the number of AFib cases in patients with HF. To determine the incidence of AFib in HF patients, additional data will be extracted on the number of new cases of AFib among patients with HF. Finally, data will be extracted on the mean duration of follow up, the number of death due to any cause among patients with HF, and the number of deaths due to any cause among HF patients with AFib in order to determine proportion of all-cause mortality among HF patients with AFib.

For multinational studies, data on the outcome of interest will be disaggregated according to the countries in which the study was conducted. Otherwise, these studies will be presented as a single study and the countries where the study was conducted in will be highlighted. The extracted data will be cross-checked at least once by two authors (LNA and VNA) for consistency and obvious errors.

A duplicate of the online data abstraction form will be created for both authors responsible for data extraction (CMM and SNP), while the consistency of the extracted data will be monitored online by a third author (LNA) who will conduct the statistical analysis. Disagreements among authors will be resolved through consensus.

Assessment of methodological quality and risk of bias.

Two reviewers (CMM and SNP) will independently assess the included full-texts for bias. The risk of bias and quality of included studies reporting on prevalence and incidence measures will be assess using the risk of bias tool for prevalence studies proposed by Hoy *et al* [20], adapted for

the purpose of this study, **supplementary file 1**. Also, the Quality In Prognosis Studies (QUIPS) tool (**supplementary file 2)** [21] will be used to evaluate the risk of bias or quality of studies reporting on the mortality rate among HF patients with AFib. Disagreements during this process will be arbitrated by a single reviewer (CD).

Data synthesis and analysis

The author, LNA, will conduct the statistical analysis. The *'meta'* package of the statistical software R (version 3.3.3, The R Foundation for statistical computing, Vienna, Austria) will be used to analyze the extracted data. Study-specific prevalence, incidence and mortality estimates will be recalculated using crude numerators and denominators from the individual studies. Using the Freeman-Tukey single arc-sine transformation, the variance of study-specific estimates will be stabilized before pooling with the random effect meta-analysis model [22]. Heterogeneity across studies will be assessed and quantified using the Cochrane's Q and I-squared (I^2) statistics, respectively [23]. Low, medium and substantial heterogeneity will be represented by I^2 values of 25%, 50% and 75% respectively [24]. A subgroup analysis using the following variables will performed in cases of substantial heterogeneity: region (western, central, southern and eastern); study type (Hospital versus community-based); study design; study area (urban, rural or both); random sampling (yes versus no); data collection (prospective versus retrospective); gender (male versus female); age group (below versus at or above the median age); cause of heart failure (valvular versus non-valvular); severity of heart failure (NYHA stage I and II versus III and IV; and EF < 35% versus ≥ 35%); type of AFib (paroxysmal, persistent or permanent); proportion of anticoagulants and beta-blocker use (as continuous variables); and study quality.

Estimates of the prevalence, incidence and all-cause mortality rates will be pooled according to the SSA region and compared using the Q-test on analysis of variance. Publication bias will be

assessed with the aid of a symmetry of forest plots and Egger's test [25]. A p-value below 10% on Egger's test will be considered statistically significant.

Presentation and reporting of results

This review will be published in accordance with the PRISMA statement [26]. With the aid of a flow diagram, the process of study screening, selection, final inclusion and reasons for study exclusion will be demonstrated. Where necessary, summary tables and forest plots will be used to display quantitative data. The risk of bias for all the included studies will be presented using narrative summaries and tables.

The prevalence and incidence of AFib among HF patients, and the mortality rate of HF patients with AFib will be reported according to the SSA region (western, eastern, southern and central), cause of HF (valvular versus non-valvular), heart failure severity (NYHA stage I and II versus III and IV; and EF < 35% versus ≥ 35%) and study type (hospital-based versus community-based).

Protocol amendments

We do not plan to modify the present protocol. However, any modification will be succinctly described in the final review.

Patient and public involvement

Patients and/or the public were not directly involved in this study.

Ethics and dissemination

Since the review is based on already published data, an ethical approval is not required. The findings of this review will be presented in conferences and peer-reviewed journals, and shared on social media such as ResearchGate, Facebook, WhatsApp and Twitter.

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Contributors: VNA conceived the study. VNA, LNA and JJN: designed the study protocol. VNA drafted the initial manuscript. LNA, FLT, CMM, SNP, CD and JJN critically revised the protocol for methodological and intellectual content. All authors read and approved the final version of the manuscript prior to submission. VNA is the guarantor of the review.

Competing interest: None.

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Data sharing statement

No additional data are available

Table 1: Search strategy for PubMed

Supplementary File 1: Quality assessment checklist for prevalence studies (adapted from Hoy *et al*)

Supplementary file 2: Adapted Quality In Prognosis Studies (QUIPS) list for scoring methodological quality of prognosis studies

Table 1: Search strategy for PubMed

SN	Search items
1.	"Heart failure"[Mesh] OR "Cardiac failure"[tiab] OR “Cardiac insufficiency” [tiab] OR “heart failure” [tiab]
2.	“Atrial fibrillation” [Mesh] OR “Atrial fibrillation” [tiab]

3. **#1 AND #2**

4. benin/ or burkina faso/ or cape verde/ or cote d'ivoire/ or gambia/ or ghana/ or guinea/ or guinea-bissau/ or liberia/ or mali/ or mauritania/ or nigeria/ or senegal/ or sierra leone/ or togo/ or ((africa*adj2 west* or benin* or burkina fas* or cape verd* or cabo verd* or ivory coast or cote d'ivoire* or gambia* or ghana* or (guinea* not pig*) or bissau or liberia* or (mali not fowl) or malian or mauritania* or nigeria* or senegal* or sierra leon* or togo*).mp. or (Lagos or Accra or Abidjan or Dakar or Abobo or Abuja or Freetown or Ouagadougou or Conakry or Lome or Bamako or Cotonou or Kumasi or Monrovia or Ibadan or Kano or Port harcourt or Benin City or Porto Novo or Niamey or Yamoussoukro or Banjul or Timbuktu or Djenne or Abomeyu or Zaria or Tamale or Jos or Cape Coast or Maidugul or Aba or Gao or Calabar or Warri or Maiduguri or Bobo Dioulasso or Parakou or Djougou or Bohicon or Sekondi Takoradi or Sunyani or Obuasi or Teshie or Tema or Sikasso or Kalabankoro or Nouakchott or Dakhlet Nouadhibou or Benin City or Port Harcourt or Ilorin or Kaduna or Enugu or Ikorodu or Onitsha or Bauchi or Akure or Abeokuta or Sokoto or Bouake or Makeni or Kaduan or Sosgbo or Osogbo or Gombe or Ilesa or Badagry or makurdi or Sagamu or Iseyin or obbomosho or Awka or Ado Ekiti or Nsukka or Ikeja or Katsina or Okene or Lafia or Minna or Ondo city or Umuahia or Calabar or Yola or Pikine or Touba or Thies Nones or Saint Louis or Kolak or Ziguinch or (San Pedro not (Spain or Mexico or Argentina or California or United States or Italy)) or Bandama or Daloa or Owerri or Kandi or Ifi or Dakar or Ogbomosho or Divo or Korhogo)).ti,ab or Exp africa, central/ or ((africa adj2 central) or angola or cameroon* or chad.mp. or tchad.mp. or congo* or DRC or equatorial guinea* or gabon* or Sao Tome or Principe or Luanda or lobito or kuito or huambo or Malanje or Douala or Yaounde or Bamenda or Garoua of Bafoussam or Nganoundere or Maroua or Kouosseri or Buena or Kumba or N'Djamena or Moundou or Bangui or Bimbo or Brazzaville or Point Noire or Kinshasa or Lubumbashi or Leopoldville or Elizabethville or Mbuji Mayi or Bakwanga or Bukavu or Costermansville or Kananga or Luluabourg or Kisangani or Stanleyville or Tshikapa or Koalwezi or Likasi or Jadotville or Goma or Kikwit or Uvira or Bunia or Mbandaka or Coquilhatville or Matadi or Butembo or Kabinda or Mwene Ditu or Isiro or Paulis or Boma or Kindu or Bata or Malabo or Libreville).ti,ab or Exp Africa, Eastern/ or ((east* adj2 africa*) or British Indian Ocean Territory or Burundi* or Comoros or Djibouti* or Eritrea* or Ethiopia* or Kenya* or Madagascar or Malawi or Mauritius or Mayotte or Mozambique or Reunion OR Rwanda* or Seychelles or Somalia* or Sudan* or Tanzania* or Uganda* or Zambia or Zimbabwe or Crozet Islands or Iles Crozet or Scattered Islands or Iles Eparses or Mwanza or Zanzibar or Eldoret or Morogoro or Hargeysa or Berbera or Nyeri or Mbeya or Machakos or Marka or Tabora or Iringa or Gondar or Meru or Geita or Musoma or Mtwara or Songea or Kigoma or Dese or Mek'ele or Bahir Dar or Jimma or Sinyanga or Korogwe or Nairobi or "Dar es Salaam" or Mombasa or Addis Ababa or Kampala or Kigali or Mogadishu or Dodomoa or Bujumbura or Nakuru or Anananarivo or Kisumu or Maputo or Asmara or Lusaka or Harare or Port Louis or Arusha or kitale or lilongwe or malindi or machakos or hargeisa or Bulawayo or Ruiru or Lamu or Kire Dawa or Kikuyu or naivasha or mwanza or tanga or nanyuki or voi or garissa or lodwar of kakamega or maralal or kitui or webuye or Axum or Nyahururu or Jinja or Kismayo

or Namanga or Mumias or Moshi or Moroni or Lokichogio or Hola or Rwenzori Mountains or Lake Victoria or Puntland* or (Adiharush or Ali-Addeh or Alinjugur or Buramino or Dadaab or Dagahaley or Dollo Ado or Fugnido or Hagadera or Hilaweyn or Ifo or Kakuma or Kambioos or Kayaka II or Kobe or Kyangwali Nakivale or Nyarugusu or Wad Sherife or Bokolmanyo or Melkadida or Rwamanja) adj5 (camp or refug*)).ti,ab or angola/ or botswana/ or lesotho/ or malawi/ or mozambique/ or namibia/ or south africa/ or swaziland/ or zambia/ or zimbabwe/ or ((africa* adj2 south*) or angola* or botswana* or lesotho* or malawi* or mozambiq* or namibia* or swaziland or zambia* or zimbabwe or Zulu or Tsonga or Xhosa or Swazi or Ndebele or Tswana or Sotho or Shona people or BaLunda or Mbundu or Ovimbundu or Chaga or Sukuma or Pretoria or Cape Town or Johannesburg or Durban or Port Elizabeth or Bloemfontein or Windhoek or Maseru or Pietermaritz or (Kimberley not Australia) or Nespruit or Soweto or Polokwane or Limpopo or Rustenburg or Mahikeng or Oudtshroom or Stellenbosch or Paarl or Gaborone or Luanda or Cabinda or Huambo or Lubango or Kuit or Malanje or Lobito or Lilongwe or Blantyre or Mzuzu or Maputo or Matola or Beira or Nampula or Chimoio or Nacala or Quelimane or Lusaka or Kitwe or Ndola or Kabwe or Copperbelt Harare or Bulawayo or Chitungwiza or Mutare or Masvingo or Monashonaland or Manicaland).ti,ab.

5. **#3 AND #4**
6. Publication date limits: from database inception to 31 August 2018, with no language restrictions

Supplementary File 1: Quality assessment checklist for prevalence studies (adapted from Hoy et al)

Name of author(s):

Year of publication:

Study title:

Risk of bias items	Risk of bias levels	Points scored
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	**Yes** (**LOW RISK**): The study's target population was a close representation of the national population.	0
	No (**HIGH RISK**): The study's target population was clearly NOT representative of the national population.	1
2. Was the sampling frame a true or close representation of the target population?	**Yes** (**LOW RISK**): The sampling frame was a true or close representation of the target population.	0
	No (**HIGH RISK**): The sampling frame was NOT a true or close representation of the target population.	1
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	**Yes** (**LOW RISK**): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (**HIGH RISK**): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	**Yes** (**LOW RISK**): The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders	0
	No (**HIGH RISK**): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders	1
5. Were data collected directly from the subjects (as opposed to a proxy)?	**Yes** (**LOW RISK**): All data were collected directly from the subjects.	0
	No (**HIGH RISK**): In some instances, data were collected from a proxy.	1
6. Was an acceptable case definition used in the study?	**Yes** (**LOW RISK**): An acceptable case definition was used.	0
	No (**HIGH RISK**): An acceptable case definition was NOT used	1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes** (**LOW RISK**): The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	0
	No (**HIGH RISK**): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collection used for all subjects?	**Yes** (**LOW RISK**): The same mode of data collection was used for all subjects.	0
	No (**HIGH RISK**): The same mode of data collection was NOT used for all subjects.	1
9. Were the numerator(s) and denominator(s) for the parameter of interest appropriate	**Yes** (**LOW RISK**): The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
	No (**HIGH RISK**): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10. Summary on the overall risk of study bias	**LOW RISK**	0-3
	MODERATE RISK	4-6
	HIGH RISK	7-9

Supplementary File 2: Adapted Quality In Prognosis Studies (QUIPS) list for scoring methodological quality of prognosis studies

Domains	Items for consideration	For each item	Quality
Study participation	a. Adequate participation in the study by eligible persons b. Description of the source population or population of interest c. Description of the baseline study sample d. Adequate description of the sampling frame and recruitment e. Adequate description of the period and place of recruitment f. Adequate description of inclusion and exclusion criteria	(+) = 3 (+/-) = 1.5 (-) = 0	High bias: 0-6 Moderate bias: 7-12 Low bias: 13-18
Study attrition	a. Adequate response rate for study participants b. Description of attempts to collect information on participants who dropped out c. Reasons for loss to follow-up are provided d. Adequate description of participants lost to follow-up e. There are no important differences between participants who completed the study and those who did not	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-8 Moderate bias: 9-16 Low bias: 17-25
PF measurement	a. A clear definition or description of the PF is provided b. Method of PF measurement is adequately valid and reliable c. Continuous variables are reported or appropriate cut points are used d. The method and setting of measurement of PF is the same for all study participants e. Adequate proportion of the study sample has complete data for the PF f. Appropriate methods of imputation are used for missing PF data	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-8 Moderate bias: 9-16 Low bias: 17-25
Outcome measurement	a. A clear definition of the outcome is provided b. Method of outcome measurement used is adequately valid and reliable c. The method and setting of outcome measurement is the same for all study participants	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-5 Moderate bias: 6-10 Low bias: 11-15
Study confounding	a. All important confounders are measured b. Clear definitions of the important confounders measured are provided c. Measurement of all important confounders is adequately valid and reliable d. The method and setting of confounding measurement are the same for all study participants e. Appropriate methods are used if imputation is used for missing confounder data f. Important potential confounders are accounted for in the study design g. Important potential confounders are accounted for in the analysis	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-12 Moderate bias: 13-24 Low bias: 25-35
Statistical analysis and reporting	a. Sufficient presentation of data to assess the adequacy of the analytic strategy b. Strategy for model building is appropriate and is based on a conceptual framework or model c. The selected statistical model is adequate for the design of the study d. There is no selective reporting of results	(+) = 5 (+/-) = 2.5 (-) = 0	High bias: 0-7 Moderate bias: 8-14 Low bias: 15-20

PF: prognostic factor

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	3
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	13
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	11
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
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	6-7
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	6, Table 1
Study records:			
Data	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7

management			
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)	7
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	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	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	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	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	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)	9-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA