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Prevalence and factors associated with medication adherence among hypertensive patients in sub-Saharan Africa: protocol for a systematic review and meta-analysis

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Keywords:	Adherence, Prevalence, associated factors, antihypertensive, sub-Saharan Africa

Prevalence and factors associated with medication adherence among hypertensive patients in sub-Saharan Africa: protocol for a systematic review and meta-analysis

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Abstract

Introduction: Hypertension is the leading cardiovascular risk factor globally, associated with a high morbidity and mortality. The high prevalence of hypertension in sub-Saharan Africa (SSA) is associated with contrastingly low awareness, treatment and control rates. Adherence to medication remains a major determinant of optimal blood pressure control. This systematic review aims to determine the prevalence and factors associated with of adherence to antihypertensive pharmacotherapy among patients with hypertension in SSA.

Methods and analysis: We will include studies published in Africa between 1 January 1997 and 30 November 2017. The following databases will be searched: PubMed, Embase, SCOPUS and Web of Science to identify potential studies without language restriction. To minimise chances of missing studies, resources specific to African literature such as WHO AFROLIB, African Index Medicus and African Journals Online (AJOL) will also be searched. Two reviewers will independently screen studies, extract data and critically appraise included studies for risk of bias, and discrepancies will be resolved by a third reviewer. A random-effects meta-analysis is planned to pool study specific estimates to obtain a summary measure presented in Forest plots. Heterogeneity of included studies will be assessed using the χ^2 test on Cochrane's Q statistic and quantified using I-squared. Publication bias will be assessed using the Egger's test and funnel plots. This protocol has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses for Protocols (PRISMA-P) 2015 statement.

Ethical and dissemination: An ethical approval is not required for the proposed study as it will be based on already published data. The end report will be presented at conferences and published in a peer-reviewed journal.

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: CRD42017079838.

Keywords: Adherence; prevalence; associated factors; antihypertensive pharmacotherapy; sub-Saharan Africa

Strengths and limitation of this study

1. To the best of the authors' knowledge, this will be the first comprehensive systematic review and meta-analysis on the prevalence and predictors of adherence to antihypertensive pharmacotherapy among patients with hypertension in SSA.
2. It is anticipated that with the largely sensitive search strategy, this systematic review will capture the maximum available studies reporting on the prevalence and predictors of adherence to antihypertensive medication and the results will be disaggregated according to the different SSA regions and type of medication adherence tool.
3. A limitation of this study might be the absence of or limited number of community-based studies on the subject.
4. Presence of substantial heterogeneity across studies done on the subject in SSA might constitute another shortcoming.

Introduction:

Hypertension is the principal risk factor for cardiovascular diseases (CVD), whose sequelae are associated with significant morbidity and mortality worldwide. Globally, hypertension accounts for about nine million deaths among the one billion adults living with the condition [1,2]. Sub-Saharan Africa (SSA) has experienced a steady increase in the prevalence of hypertension from 9.7% to 30.8% in 1990 and 2010, respectively [3]; with remarkable regional variations ranging from 15 – 70% [2–5]. This high prevalence of hypertension on the continent is associated with contrastingly low awareness, treatment and control rates [3].

Adherence, as defined by the world health organization (WHO) is "the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider" [6]. Nonadherence to pharmacologic therapy, especially in patients with chronic health conditions, is a growing concern worldwide which constitutes a major barrier to safe, cost-effective, and effective use of drugs [6]. Adherence to diet and lifestyle modifications, and antihypertensive pharmacotherapy are pivotal in achieving optimal blood pressure (BP) control; especially for patients whose BP cannot be controlled by diet and lifestyle modification alone. Congruently, an optimal BP is crucial in the prevention of complications such as heart failure, stroke, ischaemic heart disease, kidney disease and hypertension-related mortality [7–9]. Thus, improving adherence to antihypertensive pharmacotherapy is key to ameliorating outcomes in hypertensive patients. In addition, understanding the determinants of adherence to antihypertensive pharmacotherapy among patients living with hypertension in SSA is crucial in guiding policy-makers to tailor effective strategies to improve patient adherence to antihypertensive pharmacotherapy, and consequently BP control.

In a recent review by Abegaz *et al* [10], 45.3% of hypertensive patients globally were non-adherent to their antihypertensive medication, with a nonadherence rate as high as 62.5% reported among African patients on treatment for hypertension. However, it is very likely that their prevalence estimate of nonadherence to antihypertensive medications might not capture the full picture of adherence in Africa for a number of reasons. Firstly, this study had a relatively narrow window of study inclusion. Secondly, they restricted their inclusion to studies assessing medication adherence using a single tool. Thirdly, their search was limited to only two databases without any search of the existing African-specific data sources. Importantly, a rigorous critical appraisal of the quality of included studies for this review was not done. As such, the quality of evidence from this review seems wanting, coupled with the low sensitivity of their search strategy, demonstrated in the very limited number of included studies from Africa. Drivers of this medication compliance problem were similarly not explored. Taken together, their findings present significant shortcomings limiting its ability to capture a comprehensive picture of antihypertensive medication adherence in Africa.

Considering the above caveats and compelling need for comprehensive context-specific evidence to address the burden of hypertension and CVD, we decided to conduct this systematic review and meta-analysis with focus on SSA, to determine the prevalence of adherence to antihypertensive pharmacotherapy among hypertensive patients in SSA and to investigate the factors associated with medication adherence, which have hitherto not been comprehensively synthesized in SSA.

Objective

The aim of this systematic review and meta-analysis is to determine the prevalence of adherence to antihypertensive pharmacotherapy and the factors associated with medication adherence among hypertensive patients in SSA.

Review question

This review aims to answer the following questions;

1. What is the current prevalence of adherence to antihypertensive pharmacotherapy among patients with hypertension in SSA?
2. What are the factors associated with adherence to antihypertensive pharmacotherapy among patients with hypertension in SSA?

Methods and analysis

Criteria for considering studies for the review

Inclusion criteria

Studies reporting on human subjects with the criteria below will be considered for inclusion

1. Observational studies like cross-sectional, case-control and cohort studies, and randomised control trials with available data on the prevalence of and factors associated with adherence to antihypertensive pharmacotherapy among hypertensive patients residing in SSA.
2. Participants at least 18 years of age residing in SSA.
3. Study duration: All published and unpublished literature from 1 January 1997 to 30 November 2017 will be considered for the review, without any language restriction.

Exclusion criteria

The following studies will not be considered;

1. Studies conducted among participants of non-African origin, or of African origin but residing outside Africa.
2. Editorials, letters to the editor, commentaries and case-series with less than 30 participants.
3. Studies without relevant data to compute the prevalence or predictors of adherence to antihypertensive pharmacotherapy among hypertensive patients.
4. Studies with poorly defined methodologies.
5. Duplicate studies: here the most comprehensive and/or recent study with the largest sample size will be considered.
6. Studies with incomplete data, even after request from the corresponding author.

Source of information

Search strategy for identifying relevant studies

Data sources and search strategy

Using medical subject headings (MeSH) and key text words like: "adherence", "compliance", "medication", "drug" or "antihypertensive", the abstracts of published articles with relevant information on the prevalence and/or factors associated with adherence to antihypertensive pharmacotherapy among hypertensive patients in SSA will be identified through a search of PubMed, Embase, SCOPUS and Web of Science from 1 January 1997 to 30 November 2017. To minimise chances of missing relevant studies, resources specific to African literature such as WHO AFROLIB, African Index Medicus and African Journals Online (AJOL) will also be searched. To increase the sensitivity and precision of our search, the individual nomenclature of

all SSA countries will be included as additional key search terms [11]. The main search strategy for PubMed is displayed in **Table 1**.

Thereafter, potential abstracts will be reviewed and their full-texts retrieved through Embase, PubMed, Scopus, Google scholar, Sci Hub or the journal's website. After retrieving the full-texts of relevant articles and reviews on the subject, their reference lists will be examined to identify other relevant articles not captured during our search. The full-texts of these articles will be retrieved as described above.

Grey literature

Google Scholar will be used to search for grey literature. We shall also search conference websites and those of hypertension and cardiology societies in Africa like the Pan-African Society of Cardiology for relevant material. Where a full-text of an article cannot be accessed from any of the aforementioned sources, the corresponding author will be contacted via email or other platforms like Researchgate. In the absence of a response from the authors after multiple attempts, the said study will be excluded.

Study records

Data management

The studies obtained from the database searches shall be imported to EndNote V.7.4 software for removal of duplicates. The remaining articles will be uploaded to Rayyan QCRI [12], which is a web-based and mobile application that facilitates collaboration between reviewers involved in the screening and selection of studies to be finally included in a systematic review. A tool shall be developed a priori according to eligibility criteria to guide the process of study selection.

Screening

The titles and abstracts of papers retrieved from the search will be carefully screened, and the full-text of potentially eligible articles retrieved as earlier discussed. This exercise will be conducted independently by two authors (VNA and NFT), who will further review the full-texts of potential articles for final inclusion. The authors will compare their results at the end of every step of the selection process, and discrepancies will be resolved through discussion and consensus. A third author (LNA) will be consulted in case of any disagreement. In the event of unclear or ambiguous information, the corresponding author of the said study shall be contacted for clarification.

Data items and extraction

Two reviewers (VNA and NFT) shall independently extract data from the full texts of included studies using a pre-defined data extraction sheet. Any disagreements or inconsistencies shall be resolved by consensus or consultation with third reviewer (LNA). The following items shall be extracted: the last name of the first author and year of publication, year(s) the study was conducted, the country and region (Southern, Eastern, Western, and Central Africa) where the study was conducted, study design, study setting (rural versus urban), study type (community-based versus hospital-based), type of tool/method used to assess medication adherence, method of data collection (face-to-face interview versus self-administered), sample size, mean or median age and age range in years, male prevalence, total number of cases adherent to antihypertensive medication, measures of association (odds ratio (OR) or relative risk (RR)) and their respective confidence intervals) will be extracted for each factor associated with adherence to antihypertensive pharmacotherapy. For multinational studies, the prevalence of adherence to hypertensive medication will be disaggregated and reported separately for individual studies.

Where this is not possible to separate individual data for a multinational study, it will be presented as a single study, and the individual countries in which the study was conducted in highlighted.

Assessment of methodological quality and risk of bias

The risk of bias tool for prevalence studies developed by Hoy and colleagues [13] will be used to assess the quality and risk of bias among included studies (**See supplementary file 1 for Hoy et al. tool**). The risk of bias for included studies will be presented in a tabular form.

Data synthesis and analysis

The Stata software V.15 (Stata Corp V.15, Texas, U.S.A.) will be used to analyse extracted data. The Cohen's κ coefficient will be used to assess the inter-rater reliability for study inclusion [14]. A meta-analysis will be conducted for identical variables obtained from similar studies (studies using the same type of method/tool to assess adherence) to determine the pooled prevalence of adherence to antihypertensive pharmacotherapy while the predictors of adherence will be narratively reported. Assuming a binomial distribution, point estimates and appropriate denominators will be used to determine standard errors for study-specific estimates and the upper and lower bound of their confidence intervals. Using a random-effect meta-analysis model, study-specific estimates will be pooled to determine the overall prevalence estimate across studies. The Freeman-Tukey double arcsine transformation will be used to stabilise the variance of the individual studies before pooling study-specific estimates [15,16]. The Cochrane's Q statistic [17] and I^2 values will be used to assess and quantify heterogeneity across studies, respectively. I-squared values of 25%, 50% and 75% will represent low, medium and substantial heterogeneity, respectively [18]. In case of substantial heterogeneity, following variables will be

employed to investigate the source of heterogeneity using a subgroup or meta-regression analysis: age group, sex, study design (cross-sectional versus cohort studies), study setting (rural versus urban), study type (hospital-based versus community-based), type of tool/method used to assess medication adherence, method of data collection (face-to-face interview versus self-administered), geographical region (Southern, Eastern, Western, and Central Africa) and study quality. A difference between subgroups will be considered significant if the p-value is below 5%. Finally, funnel plots and Egger's test will be used to assess the presence of publication bias [19]. A p-value < 10% on Egger's test will be used to confirm the presence of publication bias. We intend to summarize the factors associated with adherence to antihypertensive medication in a narrative fashion.

Confidence in cumulative evidence

The Grading of Recommendation Assessment Development and Evaluation (GRADE) approach will be used to evaluate the strength of evidence provided by the studies included in the final review by assessing the consistency, risk of bias and publication bias. Depending on whether further research is capable of changing the effect size, likely to have considerable impact on the effect size or unlikely to change the effect size, the studies will be described as 'low', 'moderate' and 'high' quality, respectively.

Presentation and reporting of results

The PRISMA guidelines will be used to publish the proposed systematic review [20]. The PRISMA checklist will also be published alongside the final review **(Supplementary file 2)**. The entire process of study screening, selection and inclusion will be depicted with the aid of a flow diagram. Reasons for study exclusion will be documented and summary shown in the flow

diagram. Where appropriate, quantitative data will be presented using forest plots and summary tables. Additionally, tables and narrative summaries will be used to report the risk of bias for every eligible study.

Protocol amendments

We do not plan to amend this protocol. Nevertheless, in case of any modifications, these will be explicitly addressed in our final review report.

Ethical and dissemination: An ethical approval is not required for the proposed study as it will be based on already published data. The end report will be presented at conferences and published in a peer-reviewed journal.

References

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2224–60.

2. global_brief_hypertension.pdf [Internet]. [cited 2017 Sep 25]. Available from: http://ish-world.com/downloads/pdf/global_brief_hypertension.pdf

3. Adeloye D. An Estimate of the Incidence and Prevalence of Stroke in Africa: A Systematic Review and Meta-Analysis. PLOS ONE. 2014;9:e100724.

4. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. Circulation. 2016;134:441–50.

5. Ataklte F, Erqou S, Kaptoge S, Taye B, Echouffo-Tcheugui JB, Kengne AP. Burden of undiagnosed hypertension in sub-saharan Africa: a systematic review and meta-analysis. Hypertension. 2015;65:291–8.

6. Sabaté E, Project WA to LTT, Network GAI, Diseases WHOD of M of N. Adherence to long-term therapies : evidence for action. 2003 [cited 2017 Sep 25]; Available from: http://www.who.int/iris/handle/10665/42682

7. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507–20.

8. Rosendorff C, Black HR, Cannon CP, Gersh BJ, Gore J, Izzo JL, et al. Treatment of Hypertension in the Prevention and Management of Ischemic Heart Disease: A Scientific Statement From the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation. 2007;115:2761–88.

9. Špinar J. Hypertension and ischemic heart disease. Cor et Vasa. 2012;54:e433–8.

10. Abegaz TM, Shehab A, Gebreyohannes EA, Bhagavathula AS, Elnour AA. Nonadherence to antihypertensive drugs. Medicine (Baltimore) [Internet]. 2017;96. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5287944/

11. Pienaar E, Grobler L, Busgeeth K, Eisinga A, Siegfried N. Developing a geographic search filter to identify randomised controlled trials in Africa: finding the optimal balance between sensitivity and precision. Health Info Libr J. 2011;28:210–5.

12. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Systematic Reviews. 2016;5:210.

13. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65:934–9.

14. McHugh M. Interrater reliability: the kappa statistic. Biochem Med. 2012;22:276–82.

15. Miller JJ. The Inverse of the Freeman – Tukey Double Arcsine Transformation. The American Statistician. 1978;32:138–138.

16. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health. 2013;67:974–8.

17. Cochran WG. The Combination of Estimates from Different Experiments. Biometrics. 1954;10:101–29.

18. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58.

19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.

20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine. 2009;6:e1000097.

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

Competing interest: None.

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Data sharing statement

No additional data are available

Table 1: Main search strategy for PubMed.

Supplementary file 1: Risk of bias tool for prevalence studies by Hoy et al.

Supplementary file 2: PRISMA-P checklist for the current protocol.

Table 1: Main search strategy for PubMed

SN	Search items
1.	(Adherence OR compliance) OR (predictor OR 'associat* factor' OR determinant)
2.	Medication OR drug OR antihypertensive* OR "Blood pressure lowering" OR pharmacotherapy
3.	**#1 AND #2**
4.	((Africa* OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR Cameroon OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Democratic Republic of Congo" OR Djibouti OR "Equatorial Guinea" OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR "Guinea Bissau" OR "Ivory Coast" OR "Cote d'Ivoire" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "South Africa" OR "St Helena" OR Swaziland OR Tanzania OR Togo OR Uganda OR Zaire OR Zambia OR Zimbabwe OR "Central Africa" OR "Central African" OR "West Africa" OR "West African" OR "Western Africa" OR "Western African" OR "East Africa" OR "East African" OR "Eastern Africa" OR "Eastern African" OR "South African" OR "Southern Africa" OR "Southern African" OR "sub Saharan Africa" OR "sub Saharan African" OR "subSaharan Africa" OR "subSaharan African") NOT ("guinea pig" OR "guinea pigs" OR "aspergillus niger")))
5.	**#3 AND #4**
6.	Date limits: 1 January 1997 to 30 November 2017, with no language restrictions

Quality assessment checklist for prevalence studies (adapted from Hoy et al [1])

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

1. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65: 934-939.

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	12
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	11-12
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
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	4-5
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	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	7-8
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	7, Table 1
Study records:			
Data	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8

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)	8-9
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	9
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	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
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	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	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)	10-11
	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	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Evidence based practice, Pharmacology and therapeutics
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Abstract

Introduction: Hypertension is the leading cardiovascular risk factor globally, associated with a high morbidity and mortality. The high prevalence of hypertension in sub-Saharan Africa (SSA) is associated with contrastingly low awareness, treatment and control rates. Adherence to medication remains a major determinant of optimal blood pressure control. This systematic review aims to determine the prevalence, and factors associated with adherence to antihypertensive pharmacotherapy among patients with hypertension in SSA.

Methods and analysis: We will include studies published in Africa between 1 January 1997 and 30 November 2017. The following databases will be searched: PubMed, Embase, SCOPUS and Web of Science to identify potential studies without language restriction. To minimise chances of missing studies, resources specific to African literature such as WHO AFROLIB, African Index Medicus and African Journals Online (AJOL) will also be searched. Two reviewers will independently screen studies, extract data and critically appraise included studies for risk of bias, and a third reviewer will resolve discrepancies. A random-effects meta-analysis is planned to pool study specific estimates to obtain a summary measure presented in Forest plots. Heterogeneity of included studies will be assessed using the χ^2 test on Cochrane's Q statistic and quantified using I-squared. Publication bias will be assessed using the Egger's test and funnel plots. This protocol has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses for Protocols (PRISMA-P) 2015 statement.

Ethical and dissemination: An ethical approval is not required for the proposed study, as it will be based on already published data. The end report will be presented at conferences and published in a peer-reviewed journal.

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: CRD42017079838.

Keywords: Adherence; prevalence; associated factors; antihypertensive pharmacotherapy; sub-Saharan Africa

Strengths and limitation of this study

1. To the best of the authors' knowledge, this will be the first comprehensive systematic review and meta-analysis on the prevalence and predictors of adherence to antihypertensive pharmacotherapy among patients with hypertension in SSA.
2. We anticipate that with the largely sensitive search strategy, this systematic review will capture the maximum available studies reporting on the prevalence and predictors of adherence to antihypertensive medication and the results will be disaggregated according to the different SSA regions and type of method or tool used to assess medication adherence.
3. A limitation of this study might be the absence of or limited number of community-based studies on the subject.
4. There is currently no universally agreed method and/or tool used to evaluate medication adherence. Additionally, the use of arbitrary cut-off values to sometimes define adherence remain potential sources of substantial heterogeneity we anticipate, while assessing the prevalence of adherence to antihypertensive pharmacotherapy reported across studies done on the subject in SSA.

Introduction:

Hypertension is the principal risk factor for cardiovascular diseases (CVD), whose sequelae are associated with significant morbidity and mortality worldwide. Globally, hypertension accounts for about nine million deaths among the one billion adults living with the condition [1,2]. Sub-Saharan Africa (SSA) has experienced a steady increase in the prevalence of hypertension from 9.7% to 30.8% in 1990 and 2010, respectively [3]; with remarkable regional variations ranging from 15 – 70% [2–5]. This high prevalence of hypertension on the continent is associated with contrastingly low awareness, treatment and control rates [3].

Adherence, as defined by the world health organization (WHO) is "the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider" [6]. Nonadherence to pharmacologic therapy, especially in patients with chronic health conditions, is a growing concern worldwide which constitutes a major barrier to safe, cost-effective, and effective use of drugs [6]. The factors driving patients' adherence to medication are multifactorial, but can be grouped under five main domains [7] including; socioeconomic factors such as health literacy, medication cost, availability of health insurance, cultural beliefs about the illness and treatment. Secondly, factors related to the healthcare system like provider-patient relationship, provider communication skills, presence of community care and short waiting time. Third, factors related to conditions such as absence of symptoms, chronic conditions, depression and psychotic disorders. Fourth, therapy-related factors such as duration of therapy, frequency of changes in medication, absence of side effects, number of daily doses and absence of concurrent medication; and finally, patient-related factors such as motivation, good knowledge about medication and perceived benefit of treatment [7]. Adherence to diet and lifestyle modifications,

and antihypertensive pharmacotherapy are pivotal in achieving optimal blood pressure (BP) control; especially for patients whose BP cannot be controlled by diet and lifestyle modification alone. Congruently, an optimal BP is crucial in the prevention of complications such as heart failure, stroke, ischaemic heart disease, kidney disease and hypertension-related mortality [8–10]. Thus, improving adherence to antihypertensive pharmacotherapy is key to ameliorating outcomes in hypertensive patients. In addition, understanding the determinants of adherence to antihypertensive pharmacotherapy among patients living with hypertension in SSA is crucial in guiding policy-makers to tailor effective strategies to improve patient adherence to antihypertensive pharmacotherapy, and consequently BP control.

In a recent review by Abegaz *et al* [11], 45.3% of hypertensive patients globally were non-adherent to their antihypertensive medication, with a nonadherence rate as high as 62.5% reported among African patients on treatment for hypertension. However, it is very likely that their prevalence estimate of nonadherence to antihypertensive medications might not capture the full picture of adherence in Africa for a number of reasons. Firstly, this study had a relatively narrow window of study inclusion. Secondly, they restricted their inclusion to studies assessing medication adherence using a single tool. Thirdly, their search was limited to only two databases without any search of the existing African-specific data sources. Importantly, a rigorous critical appraisal of the quality of included studies for this review was not done. As such, the quality of evidence from this review seems wanting, coupled with the low sensitivity of their search strategy, demonstrated in the very limited number of included studies from Africa. Drivers of this medication compliance problem were similarly not explored. Taken together, their findings present significant shortcomings limiting its ability to capture a comprehensive picture of antihypertensive medication adherence in Africa.

Considering the above caveats and compelling need for comprehensive context-specific evidence to address the burden of hypertension and CVD, we decided to conduct this systematic review and meta-analysis with focus on SSA. Our aim is to determine the prevalence of adherence to antihypertensive pharmacotherapy among hypertensive patients in SSA and to investigate the factors associated with medication adherence, which have hitherto not been comprehensively synthesized in SSA.

Objective

The aim of this systematic review and meta-analysis is to determine the prevalence of adherence to antihypertensive pharmacotherapy and the factors associated with medication adherence among hypertensive patients in SSA.

Review question

This review aims to answer the following questions;

1. What is the current prevalence of adherence to antihypertensive pharmacotherapy among patients with hypertension in SSA?
2. What are the factors associated with adherence to antihypertensive pharmacotherapy among patients with hypertension in SSA?

Methods and analysis

Criteria for considering studies for the review

Inclusion criteria

Studies reporting on human subjects with the criteria below will be considered for inclusion

1. Observational studies with available data on the prevalence (cross-sectional, case series with at least 30 participants and cohort studies), and factors associated with adherence to antihypertensive pharmacotherapy (cross sectional, case-control, cohort and randomised control trials) among hypertensive patients residing in SSA.
2. Participants at least 18 years of age residing in SSA.
3. Publication date: All published and unpublished literature up to 31 December 2017 will be considered for the review, without any language restriction.

Exclusion criteria

The following studies will not be considered;

1. Studies conducted among participants of non-SSA origin, or of SSA origin but residing outside the region.
2. Editorials, letters to the editor, commentaries and case-series with less than 30 participants.
3. Studies without relevant data to compute the prevalence or predictors of adherence to antihypertensive pharmacotherapy among hypertensive patients.
4. Duplicate studies: here the most comprehensive and/or recent study with the largest sample size will be considered.
5. Studies with incomplete data, even after request from the corresponding author.

Source of information

Search strategy for identifying relevant studies

Data sources and search strategy

Using medical subject headings (MeSH) and key text words like, “adherence”, “compliance”, “medication”, “drug” or “antihypertensive”, the abstracts of published articles with relevant information on the prevalence and/or factors associated with adherence to antihypertensive pharmacotherapy among hypertensive patients in SSA will be identified. This will be achieved through a search of databases including PubMed, Embase, SCOPUS and Web of Science from inception to 31 December 2017. To minimise chances of missing relevant studies, resources specific to African literature such as WHO AFROLIB, African Index Medicus and African Journals Online (AJOL) will also be searched. To improve the sensitivity and precision of our search geographically, we shall use a validated search filter proposed for Africa [12]. The main search strategy for PubMed is displayed in **Table 1**.

Thereafter, potential abstracts will be reviewed and their full-texts retrieved through Embase, PubMed, Scopus, Google scholar, Sci Hub or the journal’s website. After retrieving the full-texts of relevant articles and reviews on the subject, their reference lists will be examined to identify other relevant articles not captured during our search. The full-texts of these articles will be retrieved as described above.

Grey literature

Google Scholar will be used to search for grey literature. We shall also search conference websites and those of hypertension and cardiology societies in Africa like the Pan-African Society of Cardiology for relevant material. Where a full-text of an article cannot be accessed from any of the aforementioned sources, the corresponding author will be contacted via email or other platforms like Researchgate. In the absence of a response from the authors after multiple attempts, the said study will be excluded.

Study records

Data management

The studies obtained from the database searches shall be imported to EndNote V.7.4 software for removal of duplicates. The remaining articles will be uploaded to Rayyan QCRI [13], which is a web-based and mobile application that facilitates collaboration between reviewers involved in the screening and selection of studies to be finally included in a systematic review. A tool shall be developed a priori according to eligibility criteria to guide the process of study selection.

Screening

The titles and abstracts of papers retrieved from the search will be carefully screened, and the full-text of potentially eligible articles retrieved as earlier discussed. This exercise will be conducted independently by two authors (VNA and NFT), who will further review the full-texts of potential articles for final inclusion. The authors will compare their results at every step of the selection process, and discrepancies will be resolved through discussion and consensus. A third author (LNA) will be consulted in case of any disagreement. In the event of unclear or

ambiguous information, the corresponding author of the said study shall be contacted for clarification.

Data items and extraction

Two reviewers (VNA and NFT) shall independently extract data from the full texts of included studies using a pre-defined data extraction sheet. Any disagreements or inconsistencies shall be resolved by consensus or consultation with third reviewer (LNA). Data will be extracted according to the outcome of interest: i) prevalence and ii) factors associated with adherence to antihypertensive pharmacotherapy.

a. Prevalence of adherence to antihypertensive pharmacotherapy

The following items shall be extracted: the last name of the first author and year of publication, year (s) the study was conducted, the country and region (Southern, Eastern, Western, and Central Africa) where the study was conducted, study design, study setting (rural versus urban) and study type (community-based versus hospital-based). Data on method used to assess medication adherence including self-report (using tools like *Brief Medication Questionnaire, Eight-Item Morisky Medication Adherence scale and Medication Adherence Report Scale),* or pill count, electronic monitoring, pharmacy records and prescription claims, biological assay will be collected. The approach to data collection (face-to-face interview versus self-administered), sample size, total number of cases adherent to antihypertensive medication, mean or median doses taken, mean or median age and age range in years and the male proportion in the respective studies will also be obtained.

The three different components of adherence: initiation (the time interval from prescription of antihypertensive medication until when the patient took the first dose of his medication), implementation (the time from initiation to when the patient took the last dose of his antihypertensive medications) and discontinuation (the point when the patient misses the next dose to his treatment and no further dose is taken; this marks the end of therapy) will be considered when defining adherence to antihypertensive pharmacotherapy [14].

b. Factors associated with adherence to antihypertensive pharmacotherapy

In addition to general data items obtained in the previous section, the measure of association (odds ratio (OR) or relative risk (RR) with their respective confidence intervals) for each associated factor will be extracted and specification made if obtained from a univariate or multivariate analysis. In case of multivariate analysis, the variables adjusted for will also be obtained.

Overall, for multinational studies, the prevalence of adherence to hypertensive medication as well as the associated factors will be disaggregated and reported separately for individual studies. In case it is impossible to separate individual country data for a multinational study, we will present as a single study, and the individual countries in which the study was conducted in will be highlighted.

Assessment of methodological quality and risk of bias

The risk of bias tool for prevalence studies developed by Hoy and colleagues [15] will be used to assess the quality and risk of bias among included studies reporting on the prevalence of adherence to antihypertensive pharmacotherapy (See supplementary file 1 for Hoy et al. tool).

On the other hand, the Quality In Prognosis Studies (QUIPS) tool will be used to assess the risk of bias for cohort and prognostic studies reporting the factors associated with medication adherence [16]. The risk of bias assessment will done conducted independently by two authors (VNA and NFT). The risk of bias for included studies will be presented in a tabular form.

Data synthesis and analysis

The Stata software V.15 (Stata Corp V.15, Texas, U.S.A.) will be used to analyse extracted data. The Cohen's κ coefficient will be used to assess the inter-rater reliability for study inclusion [17].

a. Prevalence of adherence to antihypertensive pharmacotherapy

A meta-analysis will be conducted for identical variables obtained from similar studies (studies using the same type of method/tool to assess adherence) to determine the pooled prevalence of adherence to antihypertensive pharmacotherapy. Assuming a binomial distribution, point estimates and appropriate denominators will be used to determine standard errors for study-specific estimates and the upper and lower bound of their confidence intervals. Using a random-effect meta-analysis model, study-specific estimates will be pooled to determine the overall prevalence estimate across studies. The Freeman-Tukey double arcsine transformation will be used to stabilise the variance of the individual studies before pooling study-specific estimates [18]. The Cochrane's Q statistic [19] and I^2 values will be used to assess and quantify heterogeneity across studies, respectively. I-squared values of 25%, 50% and 75% will represent low, medium and substantial heterogeneity, respectively [20]. In case of substantial clinical and/ or methodological heterogeneity, we will perform a subgroup analysis using the following variables: age group (below versus at or above the median), sex (male versus female), comorbidities (presence versus absence) and duration of treatment (below versus at or above the

median). Other variables that will be investigated include: study design (cross-sectional versus cohort studies), study setting (rural versus urban), study type (hospital-based versus community-based), tool used to evaluate adherence, method used to assess medication adherence, method of data collection (face-to-face interview versus self-administered), geographical region (Southern, Eastern, Western, and Central Africa) and study quality. A difference between subgroups will be considered significant if the p-value is below 5%. Finally, funnel plots and Egger's test will be used to assess the presence of publication bias [21]. A p-value < 10% on Egger's test will be used to confirm the presence of publication bias.

b. Factors associated with adherence to antihypertensive pharmacotherapy

It is anticipated that there will be significant variation in factors associated with adherence to antihypertensive medication that have been investigated either clinically or methodologically/statistically. As such, pooling such data may put to question the reliability of the final summary estimate. Available data on these identified factors will thus be summarized in tabular form accompanied with a narrative discussion.

Confidence in cumulative evidence

The Grading of Recommendation Assessment Development and Evaluation (GRADE) approach will be used to evaluate the strength of evidence provided by the studies included in the final review by assessing the consistency, risk of bias and publication bias. Depending on whether further research is capable of changing the effect size, likely to have considerable impact on the effect size or unlikely to change the effect size, the studies will be described as 'low', 'moderate' and 'high' quality, respectively.

Presentation and reporting of results

The PRISMA guidelines will be used to publish the proposed systematic review [22]. The PRISMA checklist will also be published alongside the final review **(Supplementary file 2)**. The entire process of study screening, selection and inclusion will be depicted with the aid of a flow diagram. Reasons for study exclusion will be documented and summary shown in the flow diagram. Where appropriate, quantitative data will be presented on forest plots and summary tables.

The prevalence of adherence to antihypertensive pharmacotherapy will be reported according to the study setting (hospital-based versus community-based study), tool (e.g. Brief Medication Questionnaire, Eight-Item Morisky Medication Adherence scale and Medication Adherence Report Scale) and method used to evaluate medication adherence. Additionally, tables and narrative summaries will be used to report the risk of bias for every eligible study.

Protocol amendments

We do not plan to amend this protocol. Nevertheless, in case of any modifications, these will be explicitly addressed in our final review report.

Ethical and dissemination: An ethical approval is not required for the proposed study as it will be based on already published data. The end report will be presented at conferences and published in a peer-reviewed journal.

References

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2224–60.

2. global_brief_hypertension.pdf [Internet]. [cited 2017 Sep 25]. Available from: http://ish-world.com/downloads/pdf/global_brief_hypertension.pdf

3. Adeloye D. An Estimate of the Incidence and Prevalence of Stroke in Africa: A Systematic Review and Meta-Analysis. PLOS ONE. 2014;9:e100724.

4. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. Circulation. 2016;134:441–50.

5. Ataklte F, Erqou S, Kaptoge S, Taye B, Echouffo-Tcheugui JB, Kengne AP. Burden of undiagnosed hypertension in sub-saharan Africa: a systematic review and meta-analysis. Hypertension. 2015;65:291–8.

6. Sabaté E, Project WA to LTT, Network GAI, Diseases WHOD of M of N. Adherence to long-term therapies : evidence for action. 2003 [cited 2017 Sep 25]; Available from: http://www.who.int/iris/handle/10665/42682

7. Ferdinand K, Senatore F, Clayton-Jeter H, Cryer D, Lewin J, Nasser S, et al. Improving Medication Adherence in Cardiometabolic Disease. JACC. 2017;69:437–51.

8. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507–20.

9. Rosendorff C, Black HR, Cannon CP, Gersh BJ, Gore J, Izzo JL, et al. Treatment of Hypertension in the Prevention and Management of Ischemic Heart Disease: A Scientific Statement From the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation. 2007;115:2761–88.

10. Špinar J. Hypertension and ischemic heart disease. Cor et Vasa. 2012;54:e433–8.

11. Abegaz TM, Shehab A, Gebreyohannes EA, Bhagavathula AS, Elnour AA. Nonadherence to antihypertensive drugs. Medicine (Baltimore) [Internet]. 2017;96. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5287944/

12. Sandy C. Health Sciences Search Filters: Geographic Filters for Africa. Edmonton, AB: University of Alberta; 2017. Available from: https://guides.library.ualberta.ca/c.php?g=342568&p=4521604

13. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Systematic Reviews. 2016;5:210.

14. Vrijens B, Geest SD, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. British Journal of Clinical Pharmacology. 2012;73:691.

15. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65:934–9.

16. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing Bias in Studies of Prognostic Factors. Annals of Internal Medicine. 2013;158:280.

17. McHugh M. Interrater reliability: the kappa statistic. Biochem Med. 2012;22:276–82.

18. Miller JJ. The Inverse of the Freeman – Tukey Double Arcsine Transformation. The American Statistician. 1978;32:138–138.

19. Cochran WG. The Combination of Estimates from Different Experiments. Biometrics. 1954;10:101–29.

20. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58.

21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.

22. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine. 2009;6:e1000097.

Contributors: LNA conceived the study. VNA, NFT, LNA designed the study protocol. VNA drafted the initial manuscript. NFT and LNA critically revised the protocol for methodological

and intellectual content: LNA is the guarantor of the review. All authors read and approved the final version of the manuscript prior to submission.

Competing interest: None.

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Data sharing statement

No additional data are available

Table 1: Main search strategy for PubMed.

Supplementary file 1: Hoy Risk of bias tool for prevalence studies

Supplementary file 2: PRISMA-P checklist for the current protocol.

Table 1: Main search strategy for PubMed

SN	Search items
1.	"Medication Adherence"[Mesh] AND "Patient Compliance"[Mesh] OR adherence or compliance OR (predictor OR 'associat* factor' OR determinant)
2.	Antihypertensive Agents"[Mesh] OR antihypertensive* or 'blood pressure lowering' or 'antihypertensive pharmacotherapy'
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

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	12
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	11-12
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
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	4-5
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	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	7-8
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	7, Table 1
Study records:			
Data	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8

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)	8-9
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	9
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	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
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	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	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)	10-11
	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	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

BMJ Open

Prevalence and factors associated with medication adherence among hypertensive patients in sub-Saharan Africa: protocol for a systematic review and meta-analysis

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Prevalence and factors associated with medication adherence among hypertensive patients in sub-Saharan Africa: protocol for a systematic review and meta-analysis

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Word count: Abstract: 291 Text: 3555

Abstract

Introduction: Hypertension is the leading cardiovascular risk factor globally, associated with a high morbidity and mortality. The high prevalence of hypertension in sub-Saharan Africa (SSA) is associated with contrastingly low awareness, treatment and control rates. Adherence to medication remains a major determinant of optimal blood pressure control. This systematic review aims to determine the prevalence, and factors associated with adherence to antihypertensive pharmacotherapy among patients with hypertension in SSA.

Methods and analysis: We will include studies published in Africa up to 31 December 2017. The following databases will be searched: PubMed, Embase, SCOPUS and Web of Science to identify potential studies without language restriction. To minimise chances of missing studies, resources specific to African literature such as WHO AFROLIB, African Index Medicus and African Journals Online (AJOL) will also be searched. Two reviewers will independently screen studies, extract data and critically appraise included studies for risk of bias, and a third reviewer will resolve discrepancies. A random-effects meta-analysis is planned to pool study specific estimates to obtain a summary measure presented in Forest plots. Heterogeneity of included studies will be assessed using the χ^2 test on Cochrane's Q statistic and quantified using I-squared. Publication bias will be assessed using the Egger's test and funnel plots. This protocol has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses for Protocols (PRISMA-P) 2015 statement.

Ethical and dissemination: An ethical approval is not required for the proposed study, as it will be based on already published data. The end report will be presented at conferences and published in a peer-reviewed journal.

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: CRD42017079838.

Keywords: Adherence; prevalence; associated factors; antihypertensive pharmacotherapy; sub-Saharan Africa

Strengths and limitation of this study

1. To the best of the authors' knowledge, this will be the first comprehensive systematic review and meta-analysis on the prevalence and predictors of adherence to antihypertensive pharmacotherapy among patients with hypertension in SSA.
2. We anticipate that with the largely sensitive search strategy, this systematic review will capture the maximum available studies reporting on the prevalence and predictors of adherence to antihypertensive medication and the results will be disaggregated according to the different SSA regions and type of method or tool used to assess medication adherence.
3. A limitation of this study might be the absence of or limited number of community-based studies on the subject.
4. There is currently no universally agreed method and/or tool used to evaluate medication adherence. Additionally, the use of arbitrary cut-off values to sometimes define adherence remain potential sources of substantial heterogeneity we anticipate, while assessing the prevalence of adherence to antihypertensive pharmacotherapy reported across studies done on the subject in SSA.

Introduction:

Hypertension is the principal risk factor for cardiovascular diseases (CVD), whose sequelae are associated with significant morbidity and mortality worldwide. Globally, hypertension accounts for about nine million deaths among the one billion adults living with the condition [1,2]. Sub-Saharan Africa (SSA) has experienced a steady increase in the prevalence of hypertension from 9.7% to 30.8% in 1990 and 2010, respectively [3]; with remarkable regional variations ranging from 15 – 70% [2–5]. This high prevalence of hypertension on the continent is associated with contrastingly low awareness, treatment and control rates [3].

Adherence, as defined by the world health organization (WHO) is "the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider" [6]. Nonadherence to pharmacologic therapy, especially in patients with chronic health conditions, is a growing concern worldwide which constitutes a major barrier to safe, cost-effective, and effective use of drugs [6]. The factors driving patients' adherence to medication are multifactorial, but can be grouped under five main domains [7] including; socioeconomic factors such as health literacy, medication cost, availability of health insurance, cultural beliefs about the illness and treatment. Secondly, factors related to the healthcare system like provider-patient relationship, provider communication skills, presence of community care and short waiting time. Third, factors related to conditions such as absence of symptoms, chronic conditions, depression and psychotic disorders. Fourth, therapy-related factors such as duration of therapy, frequency of changes in medication, absence of side effects, number of daily doses and absence of concurrent medication; and finally, patient-related factors such as motivation, good knowledge about medication and perceived benefit of treatment [7]. Adherence to diet and lifestyle modifications,

and antihypertensive pharmacotherapy are pivotal in achieving optimal blood pressure (BP) control; especially for patients whose BP cannot be controlled by diet and lifestyle modification alone. Congruently, an optimal BP is crucial in the prevention of complications such as heart failure, stroke, ischaemic heart disease, kidney disease and hypertension-related mortality [8–10]. Thus, improving adherence to antihypertensive pharmacotherapy is key to ameliorating outcomes in hypertensive patients. In addition, understanding the determinants of adherence to antihypertensive pharmacotherapy among patients living with hypertension in SSA is crucial in guiding policy-makers to tailor effective strategies to improve patient adherence to antihypertensive pharmacotherapy, and consequently BP control.

In a recent review by Abegaz *et al* [11], 45.3% of hypertensive patients globally were non-adherent to their antihypertensive medication, with a nonadherence rate as high as 62.5% reported among African patients on treatment for hypertension. However, it is very likely that their prevalence estimate of nonadherence to antihypertensive medications might not capture the full picture of adherence in Africa for a number of reasons. Firstly, this study had a relatively narrow window of study inclusion. Secondly, they restricted their inclusion to studies assessing medication adherence using a single tool. Thirdly, their search was limited to only two databases without any search of the existing African-specific data sources. Importantly, a rigorous critical appraisal of the quality of included studies for this review was not done. As such, the quality of evidence from this review seems wanting, coupled with the low sensitivity of their search strategy, demonstrated in the very limited number of included studies from Africa. Drivers of this medication compliance problem were similarly not explored. Taken together, their findings present significant shortcomings limiting its ability to capture a comprehensive picture of antihypertensive medication adherence in Africa.

Considering the above caveats and compelling need for comprehensive context-specific evidence to address the burden of hypertension and CVD, we decided to conduct this systematic review and meta-analysis with focus on SSA. Our aim is to determine the prevalence of adherence to antihypertensive pharmacotherapy among hypertensive patients in SSA and to investigate the factors associated with medication adherence, which have hitherto not been comprehensively synthesized in SSA.

Objective

The aim of this systematic review and meta-analysis is to determine the prevalence of adherence to antihypertensive pharmacotherapy and the factors associated with medication adherence among hypertensive patients in SSA.

Review question

This review aims to answer the following questions;

1. What is the current prevalence of adherence to antihypertensive pharmacotherapy among patients with hypertension in SSA?
2. What are the factors associated with adherence to antihypertensive pharmacotherapy among patients with hypertension in SSA?

Methods and analysis

Criteria for considering studies for the review

Inclusion criteria

Studies reporting on human subjects with the criteria below will be considered for inclusion

1. Observational studies with available data on the prevalence (cross-sectional, case series with at least 30 participants and cohort studies), and factors associated with adherence to antihypertensive pharmacotherapy (cross sectional, case-control, cohort and randomised control trials) among hypertensive patients residing in SSA.
2. Participants at least 18 years of age residing in SSA.
3. Publication date: All published and unpublished literature up to 31 December 2017 will be considered for the review, without any language restriction.

Exclusion criteria

The following studies will not be considered;

1. Studies conducted among participants of non-SSA origin, or of SSA origin but residing outside the region.
2. Editorials, letters to the editor, commentaries and case-series with less than 30 participants.
3. Studies without relevant data to compute the prevalence or predictors of adherence to antihypertensive pharmacotherapy among hypertensive patients.
4. Duplicate studies: here the most comprehensive and/or recent study with the largest sample size will be considered.
5. Studies with incomplete data, even after request from the corresponding author.

Source of information

Search strategy for identifying relevant studies

Data sources and search strategy

Using medical subject headings (MeSH) and key text words like, “adherence”, “compliance”, “medication”, “drug” or “antihypertensive”, the abstracts of published articles with relevant information on the prevalence and/or factors associated with adherence to antihypertensive pharmacotherapy among hypertensive patients in SSA will be identified. This will be achieved through a search of databases including PubMed, Embase, SCOPUS and Web of Science from inception to 31 December 2017. To minimise chances of missing relevant studies, resources specific to African literature such as WHO AFROLIB, African Index Medicus and African Journals Online (AJOL) will also be searched. To improve the sensitivity and precision of our search geographically, we shall use a validated search filter proposed for Africa [12]. The main search strategy for PubMed is displayed in **Table 1**.

Thereafter, potential abstracts will be reviewed and their full-texts retrieved through Embase, PubMed, Scopus, Google scholar, Sci Hub or the journal’s website. After retrieving the full-texts of relevant articles and reviews on the subject, their reference lists will be examined to identify other relevant articles not captured during our search. The full-texts of these articles will be retrieved as described above.

Grey literature

Google Scholar will be used to search for grey literature. We shall also search conference websites and those of hypertension and cardiology societies in Africa like the Pan-African Society of Cardiology for relevant material. Where a full-text of an article cannot be accessed from any of the aforementioned sources, the corresponding author will be contacted via email or other platforms like ResearchGate. In the absence of a response from the authors after multiple attempts, the said study will be excluded.

Study records

Data management

The studies obtained from the database searches shall be imported to EndNote V.7.4 software for removal of duplicates. The remaining articles will be uploaded to Rayyan QCRI [13], which is a web-based and mobile application that facilitates collaboration between reviewers involved in the screening and selection of studies to be finally included in a systematic review. A tool shall be developed a priori according to eligibility criteria to guide the process of study selection.

Screening

The titles and abstracts of papers retrieved from the search will be carefully screened, and the full-text of potentially eligible articles retrieved as earlier discussed. This exercise will be conducted independently by two authors (VNA and NFT), who will further review the full-texts of potential articles for final inclusion. The authors will compare their results at every step of the selection process, and discrepancies will be resolved through discussion and consensus. A third author (LNA) will be consulted in case of any disagreement. In the event of unclear or

ambiguous information, the corresponding author of the said study shall be contacted for clarification.

Data items and extraction

Two reviewers (VNA and NFT) shall independently extract data from the full texts of included studies using a pre-defined data extraction sheet. Any disagreements or inconsistencies shall be resolved by consensus or consultation with third reviewer (LNA). Data will be extracted according to the outcome of interest: i) prevalence and ii) factors associated with adherence to antihypertensive pharmacotherapy.

a. Prevalence of adherence to antihypertensive pharmacotherapy

The following items shall be extracted: the last name of the first author and year of publication, year (s) the study was conducted, the country and region (Southern, Eastern, Western, and Central Africa) where the study was conducted, study design, study setting (rural versus urban) and study type (community-based versus hospital-based). Data on method used to assess medication adherence including self-report (using tools like *Brief Medication Questionnaire, Eight-Item Morisky Medication Adherence scale and Medication Adherence Report Scale),* or pill count, electronic monitoring, pharmacy records and prescription claims, biological assay will be collected. The approach to data collection (face-to-face interview versus self-administered), sample size, total number of cases adherent to antihypertensive medication, mean or median doses taken, mean or median age and age range in years and the male proportion in the respective studies will also be obtained.

The three different components of adherence: initiation (the time interval from prescription of antihypertensive medication until when the patient took the first dose of his medication), implementation (the time from initiation to when the patient took the last dose of his antihypertensive medications) and discontinuation (the point when the patient misses the next dose to his treatment and no further dose is taken; this marks the end of therapy) will be considered when defining adherence to antihypertensive pharmacotherapy [14].

b. Factors associated with adherence to antihypertensive pharmacotherapy

In addition to general data items obtained in the previous section, the measure of association (odds ratio (OR) or relative risk (RR) with their respective confidence intervals) for each associated factor will be extracted and specification made if obtained from a univariate or multivariate analysis. In case of multivariate analysis, the variables adjusted for will also be obtained.

Overall, for multinational studies, the prevalence of adherence to hypertensive medication as well as the associated factors will be disaggregated and reported separately for individual studies. In case it is impossible to separate individual country data for a multinational study, we will present as a single study, and the individual countries in which the study was conducted in will be highlighted.

Assessment of methodological quality and risk of bias

The risk of bias tool for prevalence studies developed by Hoy and colleagues [15] will be used to assess the quality and risk of bias among included studies reporting on the prevalence of adherence to antihypertensive pharmacotherapy (See supplementary file 1 for Hoy et al. tool).

On the other hand, the Quality In Prognosis Studies (QUIPS) tool will be used to assess the risk of bias for cohort and prognostic studies reporting the factors associated with medication adherence [16]. The risk of bias assessment will done conducted independently by two authors (VNA and NFT). The risk of bias for included studies will be presented in a tabular form.

Data synthesis and analysis

The Stata software V.15 (Stata Corp V.15, Texas, U.S.A.) will be used to analyse extracted data. The Cohen's κ coefficient will be used to assess the inter-rater reliability for study inclusion [17].

a. Prevalence of adherence to antihypertensive pharmacotherapy

A meta-analysis will be conducted for identical variables obtained from similar studies (studies using the same type of method/tool to assess adherence) to determine the pooled prevalence of adherence to antihypertensive pharmacotherapy. Assuming a binomial distribution, point estimates and appropriate denominators will be used to determine standard errors for study-specific estimates and the upper and lower bound of their confidence intervals. Using a random-effect meta-analysis model, study-specific estimates will be pooled to determine the overall prevalence estimate across studies. The Freeman-Tukey double arcsine transformation will be used to stabilise the variance of the individual studies before pooling study-specific estimates [18]. The Cochrane's Q statistic [19] and I^2 values will be used to assess and quantify heterogeneity across studies, respectively. I-squared values of 25%, 50% and 75% will represent low, medium and substantial heterogeneity, respectively [20]. In case of substantial clinical and/ or methodological heterogeneity, we will perform a subgroup analysis using the following variables: age group (below versus at or above the median), sex (male versus female), comorbidities (presence versus absence) and duration of treatment (below versus at or above the

median). Other variables that will be investigated include: study design (cross-sectional versus cohort studies), study setting (rural versus urban), study type (hospital-based versus community-based), tool used to evaluate adherence, method used to assess medication adherence, method of data collection (face-to-face interview versus self-administered), geographical region (Southern, Eastern, Western, and Central Africa) and study quality. A difference between subgroups will be considered significant if the p-value is below 5%. Finally, funnel plots and Egger's test will be used to assess the presence of publication bias [21]. A p-value < 10% on Egger's test will be used to confirm the presence of publication bias.

b. Factors associated with adherence to antihypertensive pharmacotherapy

It is anticipated that there will be significant variation in factors associated with adherence to antihypertensive medication that have been investigated either clinically or methodologically/statistically. As such, pooling such data may put to question the reliability of the final summary estimate. Available data on these identified factors will thus be summarized in tabular form accompanied with a narrative discussion.

Confidence in cumulative evidence

The Grading of Recommendation Assessment Development and Evaluation (GRADE) approach will be used to evaluate the strength of evidence provided by the studies included in the final review by assessing the consistency, risk of bias and publication bias. Depending on whether further research is capable of changing the effect size, likely to have considerable impact on the effect size or unlikely to change the effect size, the studies will be described as 'low', 'moderate' and 'high' quality, respectively.

Presentation and reporting of results

The PRISMA guidelines will be used to publish the proposed systematic review [22]. The PRISMA checklist will also be published alongside the final review **(Supplementary file 2)**. The entire process of study screening, selection and inclusion will be depicted with the aid of a flow diagram. Reasons for study exclusion will be documented and summary shown in the flow diagram. Where appropriate, quantitative data will be presented on forest plots and summary tables.

The prevalence of adherence to antihypertensive pharmacotherapy will be reported according to the study setting (hospital-based versus community-based study), tool (e.g. Brief Medication Questionnaire, Eight-Item Morisky Medication Adherence scale and Medication Adherence Report Scale) and method used to evaluate medication adherence. Additionally, tables and narrative summaries will be used to report the risk of bias for every eligible study.

Protocol amendments

We do not plan to amend this protocol. Nevertheless, in case of any modifications, these will be explicitly addressed in our final review report.

Ethical and dissemination: An ethical approval is not required for the proposed study as it will be based on already published data. The end report will be presented at conferences and published in a peer-reviewed journal.

References

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2224–60.

2. global_brief_hypertension.pdf [Internet]. [cited 2017 Sep 25]. Available from: http://ish-world.com/downloads/pdf/global_brief_hypertension.pdf

3. Adeloye D. An Estimate of the Incidence and Prevalence of Stroke in Africa: A Systematic Review and Meta-Analysis. PLOS ONE. 2014;9:e100724.

4. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. Circulation. 2016;134:441–50.

5. Ataklte F, Erqou S, Kaptoge S, Taye B, Echouffo-Tcheugui JB, Kengne AP. Burden of undiagnosed hypertension in sub-saharan Africa: a systematic review and meta-analysis. Hypertension. 2015;65:291–8.

6. Sabaté E, Project WA to LTT, Network GAI, Diseases WHOD of M of N. Adherence to long-term therapies : evidence for action. 2003 [cited 2017 Sep 25]; Available from: http://www.who.int/iris/handle/10665/42682

7. Ferdinand K, Senatore F, Clayton-Jeter H, Cryer D, Lewin J, Nasser S, et al. Improving Medication Adherence in Cardiometabolic Disease. JACC. 2017;69:437–51.

8. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507–20.

9. Rosendorff C, Black HR, Cannon CP, Gersh BJ, Gore J, Izzo JL, et al. Treatment of Hypertension in the Prevention and Management of Ischemic Heart Disease: A Scientific Statement From the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation. 2007;115:2761–88.

10. Špinar J. Hypertension and ischemic heart disease. Cor et Vasa. 2012;54:e433–8.

11. Abegaz TM, Shehab A, Gebreyohannes EA, Bhagavathula AS, Elnour AA. Nonadherence to antihypertensive drugs. Medicine (Baltimore) [Internet]. 2017;96. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5287944/

12. Sandy C. Health Sciences Search Filters: Geographic Filters for Africa. Edmonton, AB: University of Alberta; 2017. Available from: https://guides.library.ualberta.ca/c.php?g=342568&p=4521604

13. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Systematic Reviews. 2016;5:210.

14. Vrijens B, Geest SD, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. British Journal of Clinical Pharmacology. 2012;73:691.

15. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65:934–9.

16. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing Bias in Studies of Prognostic Factors. Annals of Internal Medicine. 2013;158:280.

17. McHugh M. Interrater reliability: the kappa statistic. Biochem Med. 2012;22:276–82.

18. Miller JJ. The Inverse of the Freeman – Tukey Double Arcsine Transformation. The American Statistician. 1978;32:138–138.

19. Cochran WG. The Combination of Estimates from Different Experiments. Biometrics. 1954;10:101–29.

20. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58.

21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.

22. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine. 2009;6:e1000097.

Contributors: LNA conceived the study. VNA, NFT, LNA designed the study protocol. VNA drafted the initial manuscript. NFT and LNA critically revised the protocol for methodological

and intellectual content: LNA is the guarantor of the review. All authors read and approved the final version of the manuscript prior to submission.

Competing interest: None.

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Data sharing statement

No additional data are available

Table 1: Main search strategy for PubMed.

Supplementary file 1: Hoy Risk of bias tool for prevalence studies

Supplementary file 2: PRISMA-P checklist for the current protocol.

Table 1: Main search strategy for PubMed

SN	Search items
1.	"Medication Adherence"[Mesh] AND "Patient Compliance"[Mesh] OR adherence or compliance OR (predictor OR 'associat* factor' OR determinant)
2.	Antihypertensive Agents"[Mesh] OR antihypertensive* or 'blood pressure lowering' or 'antihypertensive pharmacotherapy'
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

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	12
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	11-12
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
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	4-5
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	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	7-8
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	7, Table 1
Study records:			
Data	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8

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)	8-9
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	9
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	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
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	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	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)	10-11
	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	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11