

BMJ Open Epidemiology of venous thromboembolism in Africa: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Venous thromboembolism (VTE) is among the three major causes of cardiovascular diseases worldwide after ischaemic heart disease and stroke. Knowledge on the global epidemiology of this condition is deficient in Africa. Accurate data are needed to evaluate the burden of VTE in Africa to design effective preventive and treatment strategies. This systematic review and meta-analysis aims to summarise epidemiological data on VTE in Africa and to evaluate the use of prophylaxis in African patients at risk of VTE.

Methods and analysis Medline, Embase, Scopus and African Journal Online will be searched for relevant abstracts of studies published between 1 January 1986 and 5 December 2016, without language restriction. After a screening of abstracts, study selection, data extraction and assessment of the risk of bias, we shall assess studies individually for clinical and statistical heterogeneity. Appropriate meta-analytic techniques will then be used to pool studies judged to be clinically homogeneous. Funnel-plots analysis and Egger's test will be used to detect publication bias. Results will be presented by geographical region (Central, Eastern, Northern, Southern and Western Africa). This systematic review will be reported according to the Meta-analysis of Observational Studies in Epidemiology Guidelines.

Ethics and dissemination The current study will be based on published data, and thus ethics consideration is not required. This review is expected to provide relevant data to help in quantifying the magnitude of this disease in Africa. The final report of this study will be published in a peer-reviewed journal and the findings will be submitted to relevant health authorities.

Trial registration number The protocol for this review has been published in the International Prospective Register of systematic reviews (<http://www.crd.york.ac.uk/PROSPERO>), registration number: PROSPERO CRD42017056253.

INTRODUCTION

The recent increase in life expectancy has led to an epidemiological transition from communicable to non-communicable diseases worldwide.¹ As a result, Africa faces

Strengths and limitations of this study

- To the best of our knowledge, this will be the first systematic review and meta-analysis to summarise available data on venous thromboembolism (VTE) on the African continent.
- A limited amount of data with predominance of hospital-based studies pose as a major restriction to this study, as the result may not reflect the true burden of VTE in the general African population.
- Another possible limitation may be heterogeneity of studies done on the topic in Africa.

a growing epidemic of non-communicable diseases among which cardiovascular diseases (CVDs) remain the most frequent and a major cause of disease-associated mortality.^{2 3} In 2012, the WHO estimated that CVDs were responsible for 17.5 million deaths globally, with over three quarters occurring in low and middle-income countries, such as those in Africa.^{4 5} Although the increasing burden of CVDs in recent years has been attributed to an increase in the prevalence of atherosclerotic diseases, venous thromboembolic diseases (VTEs) still remain a major cause of CVD burden. VTEs englobe two main entities: deep vein thrombosis (DVT) and pulmonary embolism (PE); and is among the three major causes of CVDs worldwide after ischaemic heart disease and stroke.⁶ VTE is a life-threatening condition associated with significant morbidity and mortality. Usually, DVT and PE occur as postoperative complications, affecting about 33% of patients undergoing an elective general surgical procedure.⁷ Nevertheless, it complicates many medical conditions especially in patients admitted to the intensive care unit.⁷ VTEs have various clinical presentations, and the disease severity depends on the size of the occluded vessel, the length, location and duration of obstruction.

Among these locations, DVT of leg veins remains the most frequent, while PE and thrombosis of deep pelvic veins are considered the most common cause of death.⁶ Some previous systematic reviews have evaluated the burden of venous thromboembolism (VTE) in various populations including the general population⁸ and in patients with various medical conditions such as autoimmune diseases,^{9–12} liver disease,¹³ heart failure,¹⁴ diabetes mellitus,^{15,16} cancer,¹⁷ posthaematopoietic stem cell transplantation,¹⁸ postsurgery¹⁹ and during pregnancy.^{20,21} However, all these reviews summarised data mostly from populations outside Africa. As African populations differ from those of the rest of the world by their genetic background, specific living conditions in Africa including limited access to medical care, diagnosis and preventive interventions for VTEs, the burden of VTE might be different in African populations. Hence, this review seeks to provide a comprehensive overview of epidemiology of VTE and its prophylaxis in African populations.

OBJECTIVE

The aim of this study is to conduct a systematic review and meta-analysis, with the aim to determine the prevalence, incidence, mortality and prophylactic measures of VTE in Africa.

REVIEW QUESTIONS

Specifically, this review seek to answer the following questions:

1. What is the prevalence and/or incidence of VTE among African populations?
2. What is the mortality related to PE in Africa?
3. What is the proportion of subjects at risk receiving VTE prophylaxis in African?

METHODS AND ANALYSIS

This protocol is written in accordance with recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement.²²

Criteria for considering studies for the review

Inclusion criteria

1. All observational studies (cross-sectional, case series with at least 30 participants, case-control and cohort studies);
2. Published between 1 January 1986 and 5 December 2016;
3. Observational studies with sufficient data on: the prevalence and/or incidence of VTE, mortality rate of PE and use of VTE prophylaxis in African countries will be included without any language restrictions;
4. Studies published in English or French.

Exclusion criteria

We will not consider:

1. Studies conducted among populations of African origin residing outside Africa;
2. Studies in which relevant data on VTE is lacking or impossible to extract;
3. Letters, reviews, commentaries and editorials;
4. Studies with inaccessible full text either online or from the corresponding author;
5. For duplicates of studies published in more than report, the most comprehensive one reporting the largest sample size will be considered.

Search strategy for identifying relevant studies

The search strategy will be devised in two steps

Bibliographic database searches

Relevant studies published on VTE in Africa will be searched via Medline, Embase, Scopus and African Journal online (AJOL) databases from 1 January 1986 to 5 December 2016, with no language restriction. Both text words and medical subject heading terms related to VTE will be used (table 1). The individual country names for the 54 African countries will be used as additional key search terms to increase the sensitivity of our search.²³

Second, the abstracts of all eligible articles will be reviewed and full-text articles will be accessed through PubMed, Embase, Scopus Database, AJOL, Google Scholar, Health InterNetwork Access to Research Initiative (HINARI), Sci Hub or journals' websites. The authors of papers whose full text cannot be obtained by the numerous internet-based sources will be directly contacted to provide them.

Searching for others sources

The references of all relevant articles and reviews will be scrutinised for additional data sources missed during our search, and their full texts will be retrieved as detailed above.

Selection of studies for inclusion in the review

Two authors (CD and MNT) will independently assess eligible papers using an assessment guide to ensure that the selection criteria are reliably applied by all the team. These authors will carefully screen the titles and abstracts of papers obtained from the search, after which the full texts of potentially eligible papers will be retrieved by at least one author. Thereafter, they will independently review the full text of each potentially eligible study, compare their results and resolve any discrepancy by discussion and consensus. If a decision is not reached, a third review author (ATT) will be consulted for arbitration.

Assessment of methodological quality and reporting of data

An adapted version of the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al*²⁴ will be used to evaluate included studies for quality and bias, and will be applied to screened full-text articles. Assessment of the risk of selection and attrition bias will use the Cochrane guidelines available in Review Manager V.5.3 (<http://>

Table 1 Search strategy for PubMed

Search	Search terms
#1	Venous thromboembolism (tw) OR Venous thromboembolic disease(tw) Or Deep vein thrombosis(tw) Or Pulmonary embolism(tw) OR Pulmonary Thromboembolism(MeSH terms) OR Thromboembolism (MeSH terms)
#2	(Africa* OR Algeria OR Angola 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 Egypt 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 Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco 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 'South Sudan' OR 'St Helena' OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR 'Western Sahara' 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 'North Africa' OR 'North African' OR 'Northern Africa' OR 'Northern 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')
#3	#1 and #2

tech.cochrane.org/revman). Furthermore, the reporting quality of each study will be assessed using the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

Data extraction and management

A data extraction sheet will be used to collect information on the last name of the first author, year of publication, region (Central, Eastern, Northern, Southern and Western Africa), country, study design, study area (rural versus urban), study setting (population-based vs hospital based), sample size, mean or median age, age range and male prevalence, disease specific to the study population (patients with cirrhosis, patients with tuberculosis, pregnant and postpartum women and postoperative patients), the total number of cases of VTE, number of new cases and/or number of deaths due to VTE in the study population. We shall report data on DVT and PE separately. Data on the number of patients at risk of VTE who did or did not receive prophylaxis for VTE will be extracted. For multinational studies, the prevalence, incidence or mortality will be reported for the individual countries. Where it is impossible to disaggregate data of multinational studies by country, the study will be presented as one and the countries in which the study was done will be highlighted.

Data synthesis and analysis

After data collection, a meta-analysis will be conducted for identical variables. Standard errors for the study-specific estimates will be determined from the point estimate and the appropriate denominators, assuming a binominal (or Poisson for incidence data) distribution. The study-specific estimates will be pooled using a random effects meta-analysis model to obtain an overall summary estimate of the prevalence and/or incidence across studies, after stabilising the variance of individual studies with the use of the Freeman-Tukey double arc-sine

transformation.²⁵ Heterogeneity will be assessed using the X^2 test on Cochrane's Q statistic²⁶ and quantified by calculating the I^2 .²⁷ Values of 25%, 50% and 75% for I^2 represent, respectively, low, medium and high heterogeneity. We will assess the presence of publication bias using funnel plots and Egger's test.²⁸ Where substantial heterogeneity is detected, a subgroup analysis will be performed to investigate the possible sources of heterogeneity using the aforementioned variables and the study quality. In case of substantial heterogeneity, a narrative summary of our findings will be done. The inter-rater agreement for study inclusion will be assessed using Cohen's κ coefficient.²⁹ Data will be analysed using Stata software V.13 (Stata Corp).

Presentation and reporting of results

The study selection process will be summarised using a flow diagram. Quantitative data will be presented in evidence tables for individual studies as well as in summary tables and forest plots where appropriate. The quality scores and risk of bias for each eligible study will be reported accordingly. This will be tabulated and accompanied by narrative summaries. This may probably demonstrate a high incidence, prevalence and morbidity of VTE in Africa and a reduced use available methods of VTE prophylaxis.

Ethics and dissemination

Ethics consideration is not required as the current study will be based on published data. This review is expected to provide relevant data to help in quantifying the magnitude of this disease in Africa. The final report of this study will be published in a peer-reviewed journal and the findings will be submitted to relevant health authorities.

Contributors CD, MNT and JJN conceived and designed the protocol. CD drafted the manuscript. MNT, ATT, VNA and JJN critically revised the manuscript for

methodological and intellectual content. JJN is the guarantor of the review. All authors approved the final version of this manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- Hunter DJ, Fineberg HV. Convergence to common purpose in global health. *N Engl J Med* 2014;370:1753–5.
- Mbewu A, Mbanya J-C, Cardiovascular Disease. In: Jamison DT, Feachem RG, Makgoba MW, *et al*, eds. *Disease and mortality in Sub-Saharan Africa*. 2nd ed. Washington, DC: World Bank, 2006. <http://www.ncbi.nlm.nih.gov/books/NBK2294/> (accessed 13 Mar 2016).
- Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation* 1998;97:596–601.
- WHO. *WHO CVD-risk management package for low-and medium-resource settings*. Geneva, Switzerland: World Health Organization, 2002.
- WHO. *Cardiovascular diseases (CVDs)*. WHO. http://www.who.int/entity/cardiovascular_diseases/en/index.html (accessed 13 Mar 2016).
- ISTH Steering Committee for World Thrombosis. Thrombosis: a major contributor to global disease burden. *J Thromb Haemost* 2014;12:1580–90.
- Snyman LC, Potgieter J. Venous thromboembolism: risk profile and management of prophylaxis in gynaecological surgery patients. *S Afr J Obstet Gynaecol* 2014;20:76.
- Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis* 2016;41:3–14.
- Ungprasert P, Srivali N, Kittanamongkolchai W. Ankylosing spondylitis and risk of venous thromboembolism: a systematic review and meta-analysis. *Lung India* 2016;33:642–5.
- Ungprasert P, Srivali N, Kittanamongkolchai W. Systemic sclerosis and risk of venous thromboembolism: a systematic review and meta-analysis. *Mod Rheumatol* 2015;28:1–5.
- Ungprasert P, Koster MJ, Thongprayoon C, *et al*. Risk of venous thromboembolism among patients with vasculitis: a systematic review and meta-analysis. *Clin Rheumatol* 2016;35:2741–7.
- Ungprasert P, Wijarnprecha K, Tanratana P. Risk of venous thromboembolism in patients with celiac disease: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2016;31:1240–5.
- Qi X, Ren W, Guo X, *et al*. Epidemiology of venous thromboembolism in patients with liver diseases: a systematic review and meta-analysis. *Intern Emerg Med* 2015;10:205–17.
- Tang L, Wu YY, Lip GY, *et al*. Heart failure and risk of venous thromboembolism: a systematic review and meta-analysis. *Lancet Haematol* 2016;3:e30–44.
- Bell EJ, Folsom AR, Lutsey PL, *et al*. Diabetes mellitus and venous thromboembolism: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2016;111:10–18.
- Gariani K, Mavrakanas T, Combescure C, *et al*. Is diabetes mellitus a risk factor for venous thromboembolism? A systematic review and meta-analysis of case-control and cohort studies. *Eur J Intern Med* 2016;28:52–8.
- Qian C, Yan H, Hu X, *et al*. Increased risk of venous thromboembolism in patients with brain tumors: A systematic review and meta-analysis. *Thromb Res* 2016;137:58–63.
- Zahid MF, Murad MH, Litzow MR, *et al*. Venous thromboembolism following hematopoietic stem cell transplantation-a systematic review and meta-analysis. *Ann Hematol* 2016;95:1457–64.
- Yeo DX, Junnarkar S, Balasubramaniam S, *et al*. Incidence of venous thromboembolism and its pharmacological prophylaxis in Asian general surgery patients: a systematic review. *World J Surg* 2015;39:150–7.
- Skeith L, Carrier M, Robinson SE, *et al*. Risk of venous thromboembolism in pregnant women with essential thrombocythemia: a systematic review and meta-analysis. *Blood* 2017;129:934–9.
- Kourilaba G, Relakis J, Kontodimas S, *et al*. A systematic review and meta-analysis of the epidemiology and burden of venous thromboembolism among pregnant women. *Int J Gynaecol Obstet* 2016;132:4–10.
- Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
- Pienaar E, Grobler L, Busgeeth K, *et al*. 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.
- Hoy D, Brooks P, Woolf A, *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.
- Miller JJ. The inverse of the Freeman-Turkey double Arcsine transformation. *Am Stat* 1978;32:138.
- Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954;10:101–29.
- Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, *et al*. Assessing heterogeneity in meta-analysis: Q statistic or I² index? *Psychol Methods* 2006;11:193–206.
- Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med* 2012;22:276–82.