Improving anticoagulation in sub-Saharan Africa – what are the challenges, and how can we overcome them?

Johannes Mouton[1], Marc Blockman[1], Christine Sekaggya-Wiltshire[2], Jerome Semakula[2], Catriona Waitt[3], Munir Pirmohamed[3,4], and Karen Cohen[5]

[1]University of Cape Town
[2]Makerere University College of Health Sciences
[3]University of Liverpool Institute of Translational Medicine
[4]University of Liverpool
[5]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa.

July 29, 2020

Abstract

Patients in sub-Saharan Africa generally have poor anticoagulation control. We review the potential reasons for this poor control, as well as the potential solutions. Challenges include the affordability and centralisation of anticoagulation care, problems with access to medicines and INR monitoring, the lack of locally-validated standardized dosing protocols, and low levels of anticoagulation knowledge among health care workers and patients. Increasing numbers of patients will need anticoagulation in the future because of the epidemiological transition in the region. We propose that locally-developed "warfarin care bundles" which address multiple anticoagulation challenges in combination may be the most appropriate solution in this setting currently.

INTRODUCTION

Anticoagulation is used to treat and prevent venous thrombosis and to prevent intracardiac thrombosis due to some structural heart diseases or dysrhythmias. Depending on the indication, treatment may be lifelong. Over-anticoagulation may result in bleeding and under-coagulation in thrombotic complications, including stroke. With the advent of direct oral anticoagulants (DOACs), there is increased choice of drugs available. However, vitamin K antagonists such as warfarin remain the most widely used oral anticoagulants, and form the focus of this article.

When using vitamin K antagonists, the degree of anticoagulation is measured by the international normalised ratio (INR), and a patient's longitudinal anticoagulation control can be described by the proportion of INRs which fall in the therapeutic range (PTR), or by the proportion of time spent in the therapeutic range (TTR), interpolating INR results for the time between actual INR measurements. Patients in sub-Saharan Africa (SSA) have poor anticoagulation control as measured by their PTR/TTR, which is evident from trials,[1–3] large multisite registries,[4,5] and smaller observational studies (Table 1).

{Table 1 here}

In this review, we explore potential reasons for this poor anticoagulation control.

METHODS

For this narrative review, we searched Pubmed and Africa-Wide Information through EBSCOhost, using index terms and free text around four themes: (1) burden of anticoagulation indications, (2) challenges

accessing anticoagulation, (3) challenges with selecting and adjusting anticoagulant dose, and (4) patient-related challenges including adherence, knowledge, attitudes, and beliefs, and genetic factors. We also searched Google and various dissertation databases for grey literature from SSA on these issues. Further reports were found by handsearching reference lists of included studies.

CHALLENGES IN THE DISEASE BURDEN

SSA is undergoing an epidemiological transition: with increasing life expectancy the increasing burden of non-communicable disease is colliding with the pre-existing burden of infectious diseases. In the context of anticoagulation, this transition is evident in the increasing prevalence of (non-valvular) atrial fibrillation (AF), adding to the large number of people requiring anticoagulation for valvular heart disease (VHD), which in SSA is still mostly caused by rheumatic heart disease (RHD).[23] This increase in indications for anticoagulation is occurring amidst an uneven distribution of limited resources. For example, there were only 57 centres in SSA capable to perform regular open heart operations in 2011/2012 (one per 15 million population); 35 of these were in South Africa.[24] Figure 1 shows some examples of SSA anticoagulation studies mentioning resource limitations.

{Figure 1 here}

A recent systematic review suggested that AF prevalence in SSA may be higher than previously thought,[33] up to 4.3% in one Ethiopian community-based survey.[34] Patients with AF in SSA have high prevalence of concomitant stroke risk factors,[33,35] and should therefore benefit from anticoagulation. However, despite clear indications for anticoagulation, it is not always implemented in SSA.[26,36–41] Indeed, in the multi-regional RELY-AF registry,[4] patients in Africa had the second-lowest use of oral anticoagulation where indicated (19%, second only to China), and the lowest TTR (33%).

RHD prevalence among school children in SSA is 1.5% to 3.0%.[42–47] In RHD registries, only two-thirds of patients with an indication for oral anticoagulation received it,[5,37,48] and INR control was in-range in only 28%.[5]

Venous thromboembolism (VTE) epidemiology in SSA has not been well described,[49] but HIV infection is a well-established risk factor, associated with a 1.5-fold increased hazard (95% confidence interval 1.1 to 2.0).[50] As the HIV pandemic epicentre, HIV-associated VTE is commonly seen in SSA. In all the studies in Table 2, HIV prevalence was higher among patients presenting with VTE than the background prevalence. Interestingly, in a Ugandan study 9% of patients on antiretroviral therapy attending routine outpatient follow-up were found to have incidental deep venous thrombosis.[51]

{Table 2 here}

CHALLENGES ACCESSING ANTICOAGULATION

Vitamin K antagonists appear on most SSA countries' essential medicine lists.[64] Warfarin is the most commonly used, followed by acenocoumarol.[64,65] Warfarin is cheap: a 5mg tablet cost 8 US cents in rural Zambia[28] or 14 US cents in Uganda.[66] However, being essential and cheap do not necessarily make medicines available or accessible.[67] Essential medicines' availability ranged from 25% in public facilities to 49% in private facilities in Cameroon,[68] and from 49% in public facilities to 71% in retail pharmacies in Malawi.[69] Anecdotally, frequent stock-outs of warfarin have been mentioned in some SSA studies.[22,29,70] To our knowledge, the only study to systematically evaluate warfarin availability in SSA was conducted in Uganda in 2017,[66] and showed that warfarin was available on the survey day at 75/100 private pharmacies, 15/23 (65%) private hospitals, and only 4/22 (18%) public hospitals, all randomly sampled.[66]

DOACs were only available in 14/33 African countries surveyed in 2018,[71] and are often beyond the means of patients and public health services. In South Africa, which has statutory private sector medicine ceiling prices, one month's supply of dabigatran, apixaban, or rivaroxaban costs the equivalent of approximately 60 hours' minimum wage.[72] To our knowledge, no DOAC has yet been shown to be cost-effective in any SSA country's public health sector.[73]

A weak medicines regulatory environment in much of SSA means that substandard and falsified medicines may be found on the market.[74] We are not aware of any SSA data on the quality of warfarin on the market, but in a medicines quality assessment across ten West and Central African countries, there was fortunately no evidence of poor quality acenocoumarol.[75]

Dedicated anticoagulation clinics (ACCs) using standardized approaches may achieve better anticoagulation control than routine models of care, where anticoagulation patients are seen as part of the general patient mix.[76–81] Such ACCs are however not common in SSA; anticoagulation is often managed in outpatient cardiology, cardio-thoracic surgery, and haemato-oncology clinics[20,32,82] or by individual health care workers who may not use standardized approaches.[27,83] Prescribers of anticoagulation are often junior with limited practice experience.[83]

A few studies investigated SSA health care workers' knowledge, attitudes, and beliefs about anticoagulation. In one such study 164 doctors and pharmacists at an Ethiopian tertiary hospital completed a self-administered questionnaire.[84] Participants' mean score on the warfarin knowledge section was 10/15 correct answers, yet only 7% identified their own lack of knowledge on warfarin as a barrier to effective patient counselling.[84] Specific knowledge gaps identified included drug-drug interactions, and the target INR range appropriate to specific indications.[84] In a second study at the same hospital, investigators directly observed the counselling pharmacists provided during warfarin dispensing and found that only 10% of patients were told what to do when they missed a dose, while interactions and side effects were discussed in only 9% and 3% of encounters, respectively.[85] In addition, just 24% of patients were given an opportunity to ask questions at the dispensing encounter, and only 40% of warfarin containers were labelled.[85] At a South African academic hospital, in 86% of admissions for over-anticoagulation with warfarin the cause of toxicity was not identified by attending clinicians.[86] Drug-drug interactions with warfarin, which went unrecognised by the attending clinicians, were retrospectively identified by study investigators in 77% of these patients.[86]

INR testing in centralised laboratories is the norm across SSA. As a result, people living in rural settings often have no access to INR monitoring. However, centralisation can even bypass people in urban settings, as illustrated in some of the examples in Figure 1. Centralised laboratory INR testing also means that results are delivered with a long turn-around time,[27] and that patients may be required to attend separate blood sampling and INR monitoring visits,[22,87] driving up the expenses they incur.

The cost of INR testing has been identified as a barrier to anticoagulation therapy in Zambian[88] and Ethiopian reports.[29] We are aware of only one study systematically investigating the availability and cost of coagulation profile testing in SSA, conducted in Uganda in 2017.[66] At randomly sampled facilities, coagulation profile testing was available at 13/22 (59%) private hospitals, and 3/22 (14%) public hospitals,[66] at a median price of US$8.30.

At least two different point-of-care (POC) INR monitors have been validated in South African patients,[89–91] and there have been reports of using POC INR monitors in ACCs in Namibia,[19] Kenya,[7,70,92,93] and Nigeria.[87] Considering only the cost per test, POC testing is more expensive than laboratory monitoring; however, it may be cost-effective in some settings.[94] In SSA, most sites that reported using POC testing received the monitors and test strips through donations, and offered POC tests at a subsidised cost to patients.[7,87,93]

CHALLENGES WITH DOSE SELECTION AND DOSE ADJUSTMENTS

Warfarin dose selection and adjustment can be divided into an initiation phase, until a stable dose and INR is achieved, and a maintenance phase, during which further dose adjustments may be required for clinical and dietary reasons. Examples of dosing guidelines made by ministries / departments of health in SSA countries are given in Table 3. Except for the South African guideline, these are vague, with a large range of warfarin initiation doses, and little detail about how often or by how much doses should be adjusted. Aside from these national guidelines, institution-specific anticoagulation protocols, guidelines, or algorithms may be in use – in one Nigerian survey 11% of clinicians reported using such guidelines in their institutions.[95] We did not find any warfarin dose initiation or dose adjustment algorithms in use in SSA that have been

validated for the local population.

{Table 3 here}

Where detailed dose adjustment algorithms do not exist, clinicians may make erroneous or even paradoxical dose adjustments. Reviews from Cameroon,[8] Ethiopia,[9,14] and Namibia[19] report dose increases after 4%-17% of supratherapeutic INRs and dose decreases after 4%-15% of subtherapeutic INRs. In addition, dose adjustments are often inappropriately large: While clinical trial evidence has shown that warfarin dose adjustments of 10-15% were associated with better outcomes,[102] the mean warfarin dose increase in one Ethiopian review was 58% in response to an INR of 1.5 to 1.9 against a target of 2.0 to 3.0.[9] In the Namibian example, more than half of patients with an INR >4 were over-corrected so that their subsequent INR was subtherapeutic.[19]

Warfarin formulations other than 5mg are frequently not available in SSA,[6,22] making precision dosing difficult. Complicated weekly dosing schedules of alternating daily dosages which often require tablet splitting (sometimes into quarters) are used, potentially compromising the actual dose taken.[103] This may in turn influence adherence and anticoagulation control. Reasons for the unavailability of alternative formulations seem to be market-related as several SSA countries' essential medicines lists follow the WHO model list which includes 1, 2, and 5mg warfarin tablets. Even so, some Kenyan evidence suggests prescribers may simply be unaware of the market availability of alternatives to 5mg tablets.[83] Also, 1mg or 2mg formulations may be priced close to 5mg tablets, making these alternative formulations less cost-effective.

PATIENT-RELATED CHALLENGES

The importance of pharmacogenetic variability on warfarin dose requirements in SSA was demonstrated in a recent systematic review.[104] For example, three variants that are more prevalent in Black Africans than in other populations, *CYP2C9*5* ,*CYP2C9*6* , and *CYP2C9*11* , affected warfarin dose requirements by -13, -8, and -5 mg/week respectively.[104]

Potential drug-drug interactions between warfarin and co-prescribed medications hinder good anticoagulation control. In SSA, antiretroviral therapy is a significant source of potential drug-drug interactions.[18,20,22,70,92,93,105] Tuberculosis is also common in SSA, and rifampicin use induces multiple cytochrome P450 isoforms resulting in a reduced warfarin effect. In a Kenyan case series of patients on concurrent rifampicin and warfarin, the median warfarin dose increase with rifampicin was 16%, but some patients required dose increases up to +441%.[106] In a Ugandan case series, patients concomitantly prescribed rifampicin, antiretroviral therapy, and warfarin had highly labile INRs and warfarin dose requirements, and it was not possible to predict the course of INR results in any individual patient.[107] In Kenya, VTE patients with advanced HIV and tuberculosis required a median 8 additional clinic visits to achieve or maintain a therapeutic INR.[108]

Despite widespread herbal medicine use in SSA[109,110] there is very little data on how this influences anticoagulation.[111,112] Nevertheless, it is plausible that some herbal medicines may interact with warfarin.

Anticoagulation patients in SSA are younger than those in high-income settings. For example, in Uganda and South Africa the median age of patients attending five anticoagulation services was 56 years,[22] and in a Kenyan service the mean age was 43 years.[20] Younger patients often show reduced adherence compared to older patients. Two possible reasons for this are that they are economically active and therefore may be unable to attend follow-up appointments, and that they may have reproductive wishes and expectations and therefore intentionally reduce their intake of a potentially teratogenic medicine.[113,114]

Four studies reporting patients' self-reported adherence to anticoagulants in SSA are summarised in Table 4. Notably, from these, fewer than half of patients considered themselves highly adherent to warfarin. One study suggested that warfarin non-availability may contribute to poor adherence.[29] In an analysis of the "care cascade" of RHD patients in Uganda, retention in care was the stage with the highest patient drop-out.[48]

{Table 4 here}

We are not aware of any studies reporting SSA patients' attitudes and beliefs about anticoagulation. A few studies (Table 5) reported on patients' anticoagulation knowledge, with generally low levels of knowledge found. Only two studies investigated whether participants' anticoagulation knowledge correlated with their anticoagulation control, and these reached conflicting results.[10,119] Levels of knowledge were generally associated with participants' level of education and with the provision of written educational materials. Topics on which participants' knowledge was low were drug and food interactions, the effect of missing a dose, the interpretation of INR values, recognizing the symptoms of over- or underdosing, contraception, and pregnancy planning.[10,82,120]

{Table 5 here}

OVERCOMING THE CHALLENGES

Overcoming the multitude of challenges faced by anticoagulation services and patients requiring anticoagulation in SSA require a multifaceted approach. "Warfarin care bundles" are effective and viable strategies, as shown in a recent network meta-analysis of anticoagulation interventions.[127] In SSA such a warfarin care bundle must include both process-centred and patient-centred activities, the exact combination of which will be specific to each setting and will depend on cost-effectiveness to guide rational allocation of limited resources. In making process changes, it will be important to leverage off existing successful systems, such as HIV treatment programmes,[128] and to ensure these changes are embedded in a quality-improvement framework, with regular feedback to patients, clinicians, and managers.

First, we would propose patient-centred anticoagulation education and adherence support. These interventions have shown benefit on patients' knowledge, adherence, and INR control in a few individual SSA studies[13,14,116] and may be of particular benefit in vulnerable populations.[129] As pharmacists and doctors are a scarce resource in Africa, these education and support tasks can be successfully shifted to mid-level health care workers.[7] SSA has extensive expertise on providing adherence support to patients with HIV, and education and adherence support for patients with non-communicable diseases should build on these already-existing systems.[130]

Process-centred activities may include decentralisation of anticoagulation services, setting up of anticoagulation clinics, improving access to warfarin (including formulations other than the 5 mg tablet), improving access to laboratory testing and/or scaling up point-of-care INR testing, task-shifting of anticoagulation care to mid-level health care workers, staff training, and implementing locally validated dose initiation and dose adjustment algorithms. Decentralised anticoagulation clinics can be successfully implemented in SSA, with improved outcomes (and better cost-effectiveness) compared to those achieved at a central referral hospital.[93] Point-of-care INR testing has also been successfully implemented in SSA, drastically decreasing the number of visits patients have to make to the clinic.[87] However, the high cost of test strips is problematic, and relying on donations and subsidies is not sustainable. Localised dose initiation and dose adjustment algorithms must consider the comorbidities and potential drug interactions that are prevalent in SSA, such as HIV, tuberculosis, antiretrovirals, antituberculosis therapy, co-trimoxazole, and herbal / traditional medicines. These algorithms must be easy to implement, for example being paper-based, and should recommend small, percentage-based dose adjustments.[102]

One example of an effective anticoagulation programme combining multiple interventions came from Rwanda.[131] In this programme, specialist non-communicable disease nurses deliver post-operative care to VHD patients in decentralised clinics. Standard dosing algorithms are used, while nurses are supervised and supported by cardiologists, using mobile communications. Adherence support, as well as financial support, is offered to patients. While this small study did not report the effect of this programme on TTR, low mortality was described, and there were no bleeding or thrombotic complications.[131]

DOACs may be a solution to some anticoagulation challenges in SSA: while they are still prohibitively expensive to most African patients and health care systems, they will in the future come off patent, and generics may be more affordable. DOACs have the benefit of being used at fixed rather than individualised doses and do not require routine monitoring.[73] However, DOACs come with their own set of challenges.

They are contra-indicated in valvular heart disease, a significant group of patients in SSA, and require dose adjustment / are contra-indicated in severe renal impairment. DOACs have shorter half-lives than warfarin, making strict adherence more critical; ironically, without regular monitoring, adherence problems may be missed in patients on DOACs.[73] DOACs are also subject to drug-drug interactions: notably for SSA, these include interactions with rifampicin and many antiretroviral agents.[132] Finally, the management of major bleeding occurring with DOACs will require specific protocols, localised for SSA.[73]

CONCLUSION

There is significant room for improvement of anticoagulation control in countries across SSA. Increasing numbers of patients will need anticoagulation in the future because of the epidemiological transition in the region. Despite the many challenges faced by patients, health care providers, and health systems in these resource-limited settings, several opportunities for improvement exist. Decentralisation of anticoagulation care, together with expanded access to medicines and monitoring, and enhanced support to practitioners and patients, are pivotal in achieving better control. Dose initiation and dose adjustment protocols that have been developed taking locally relevant factors into account can also contribute to better anticoagulation control. With the cost of DOACs still prohibitive, locally-developed "warfarin care bundles" which address multiple anticoagulation challenges in combination, particularly when they leverage off systems that are already functional in SSA, currently appear to be the most appropriate strategy to improve anticoagulation control in this setting.

FUNDING

This research was funded by the National Institute for Health Research (NIHR) (project ref:16/137/101) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care.

CONFLICT OF INTEREST

MP receives research funding from various organisations including the Governmental bodies such as the MRC, EU Commission and Health Education England. MP also received partnership funding for the following: MRC Clinical Pharmacology Training Scheme (co-funded by MRC and Roche, UCB, Eli Lilly and Novartis); a PhD studentship jointly funded by EPSRC and Astra Zeneca; and grant funding from Vistagen Therapeutics. MP also received unrestricted educational grant support for the UK Pharmacogenetics and Stratified Medicine Network from Bristol-Myers Squibb and UCB. MP held a joint grant from NIHR with MC Diagnostics for the development of a HLA panel. None of the funding MP received is related to the current paper.

The remaining authors declare no conflicts of interest.

REFERENCES

1 Singer DE, Hellkamp AS, Piccini JP, *et al.* Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from the ROCKET AF clinical trial. *J Am Heart Assoc*2013;**2** :e000067. doi:10.1161/JAHA.112.000067

2 Connolly SJ, Pogue J, Eikelboom J, *et al.* Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range.*Circulation* 2008;**118** :2029–37. doi:10.1161/CIRCULATIONAHA.107.750000

3 Wallentin L, Yusuf S, Ezekowitz MD, *et al.* Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: An analysis of the RE-LY trial. *Lancet*2010;**376** :975–83. doi:10.1016/S0140-6736(10)61194-4

4 Oldgren J, Healey JS, Ezekowitz M, *et al.* Variations in cause and management of atrial fibrillation in a

prospective registry of 15 400 emergency department patients in 46 countries: The RE-LY atrial fibrillation registry. *Circulation* 2014;**129** :1568–76. doi:10.1161/CIRCULATIONAHA.113.005451

5 Zühlke L, Engel ME, Karthikeyan G, *et al.* Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: The Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J* 2015;**36** :1115–22. doi:10.1093/eurheartj/ehu449

6 Makubi A, Lwakatare J, Nordrehaug J, *et al.* Anticoagulant Control Results among Patients with Mechanical Heart Valves at Muhimbili National hospital, Tanzania. *Tanzania Med J*2008;**23** :12–6. doi:10.4314/tmj.v23i1.39222

7 Manji I, Pastakia SD, Do AN, *et al.* Performance outcomes of a pharmacist-managed anticoagulation clinic in the rural, resource-constrained setting of Eldoret, Kenya. *J Thromb Haemost*2011;**9** :2215–20. doi:10.1111/j.1538-7836.2011.04503.x

8 Menanga A, Sibetcheu A, Chelo D, *et al.* Surveillance du Traitement par Antivitamines K chez des Patients en Fibrillation Auriculaire à Yaoundé. *Heal Sci Dis*2015;**16** :1–6.https://www.hsd-fmsb.org/index.php/hsd/article/view/487

9 Daba FB, Tadesse F, Engidawork E. Drug-related problems and potential contributing factors in the management of deep vein thrombosis.*BMC Hematol* 2016;**16** :2. doi:10.1186/s12878-016-0043-y

10 Mariita K, Maina C, Nyamu D, *et al.* Patient factors impacting on oral anticoagulation therapy among adult outpatients in a Kenyan referral hospital. *African J Pharmacol Ther*2016;**5** :193–200.http://journals.uonbi.ac.ke/ajpt/article/view/1534

11 Sadhabiriss D. *Warfarin: Time in Therapeutic Range, a Single Centre Study on Patients using Warfarin for Stroke Prevention in Non-Valvular Atrial Fibrillation and Prosthetic Heart Valves* . 2016.http://hdl.handle.net/10413/16021

12 Sonuga BO, Hellenberg DA, Cupido CS, *et al.* Profile and anticoagulation outcomes of patients on warfarin therapy in an urban hospital in Cape Town, South Africa. *African J Prim Heal Care Fam Med* 2016;**8** :a1032. doi:10.4102/phcfm.v8i1.1032

13 Ahmed NO, Osman B, Abdelhai YM, *et al.* Impact of clinical pharmacist intervention in anticoagulation clinic in Sudan. *Int J Clin Pharm* 2017;**39** :769–73. doi:10.1007/s11096-017-0475-x

14 Fenta TG, Assefa T, Alemayehu B. Quality of anticoagulation management with warfarin among outpatients in a tertiary hospital in Addis Ababa, Ethiopia: a retrospective cross-sectional study. *BMC Health Serv Res* 2017;**17** :389. doi:10.1186/s12913-017-2330-0

15 Nyamu DG, Guantai AN, Osanjo GO, *et al.* Predictors of Adequate Ambulatory Anticoagulation among Adult Patients in a Tertiary Teaching and Referral Hospital in Kenya. *African J Pharmacol Ther*2017;**6** :20–6.http://journals.uonbi.ac.ke/ajpt/article/view/1549

16 Coulibaly I, Diatema S, Hauhouot-Attoungbre M. Quality of oral anticoagulation with Vitamin K antagonists assessed by the TTR in ambulatory non-valvular atrial fibrillation patients (NVAF) at Abidjan Institute of Cardiology. *Trop Cardiol* Published Online First: 2018.http://tropical-cardiology.com/Accueil/index.php/fr/2013-08-10-06-44-55/n-153-juil-aout-sep-2018/356-qualite-de-l-anticoagulation-orale-par-antivitamine-k-evaluee-par-le-calcul-du-ttr-chez-des-patients-traites-en-ambulatoire-pour-fibrillation-auriculaire-

17 Ebrahim I, Bryer A, Cohen K, *et al.* Poor anticoagulation control in patients taking warfarin at a tertiary and district-level prothrombin clinic in Cape Town, South Africa. *South African Med J* 2018;**108** :490–4. doi:10.7196/SAMJ.2018.v108i6.13062

18 Mwita JC, Francis JM, Oyekunle AA, *et al.* Quality of Anticoagulation With Warfarin at a Tertiary Hospital in Botswana.*Clin Appl Thromb* 2018;**24** :596–601. doi:10.1177/1076029617747413

19 Jonkman LJ, Gwanyanya MP, Kakololo MN, *et al.* Assessment of anticoagulation management in outpatients attending a warfarin clinic in Windhoek, Namibia. *Drugs Ther Perspect* 2019;**35** :341–6. doi:10.1007/s40267-019-00630-y

20 Karuri S, Nyamu D, Opanga S, *et al.* Factors Associated with Time in Therapeutic Range among Patients on Oral Anticoagulation Therapy in a Tertiary Teaching and Referral Hospital in Kenya. *East Cent African J Pharm Sci*2019;**22** :85–95.http://uonjournals.uonbi.ac.ke/ojs/index.php/ecajps/article/view/293

21 Botsile E, Mwita JC. Incidence and risk factors for thromboembolism and major bleeding in patients with mechanical heart valves: a tertiary hospital-based study in Botswana. *Cardiovasc J Afr* 2020;:1–5. doi:10.5830/CVJA-2020-006

22 Semakula JR, Mouton JP, Jorgensen A, *et al.* A cross-sectional evaluation of five warfarin anticoagulation services in Uganda and South Africa. *PLoS One* 2020;**15** :e0227458. doi:10.1371/journal.pone.0227458

23 Rwebembera J, Manyilirah W, Zhu ZW, *et al.* Prevalence and characteristics of primary left-sided valve disease in a cohort of 15,000 patients undergoing echocardiography studies in a tertiary hospital in Uganda. *BMC Cardiovasc Disord* 2018;**18** :82. doi:10.1186/s12872-018-0813-5

24 Yankah C, Fynn-Thompson F, Antunes M, *et al.* Cardiac surgery capacity in sub-Saharan Africa: Quo Vadis? *Thorac Cardiovasc Surg*2014;**62** :393–401. doi:10.1055/s-0034-1383723

25 Mandi DG, Bamouni J, Naïbé DT, *et al.* Epidemiology and long-term prognosis of atrial fibrillation in rural African patients.*Egypt Hear J* 2019;**71** :6. doi:10.1186/s43044-019-0005-3

26 Yameogo AR, Kologo JK, Mandi G, *et al.* Use of Vitamins K antagonists in non-valvular atrial fibrillation thromboembolic risk prevention in Burkina Faso. *Pan Afr Med J* 2016;**24** :108. doi:10.11604/pamj.2016.24.108.7100

27 Anakwue R, Ocheni S, Madu A. Utilization of oral anticoagulation in a teaching hospital in Nigeria. *Ann Med Health Sci Res*2014;**4** :286–90. doi:10.4103/2141-9248.141973

28 Alcheikh A, Chawe A, Kowa SF, *et al.* A comprehensive approach to improving laboratory services in rural Zambia. *Blood Adv*2019;**3** :11–5. doi:10.1182/bloodadvances.2019gs121633

29 Chalachew T, Yadeta D, Tefera E. Factors associated with sub-optimal control of anticoagulation in patients with prosthetic heart valves taking oral anticoagulants in a sub-Saharan African setting.*Cardiovasc J Afr* 2019;**30** :317–20. doi:10.5830/cvja-2019-024

30 Raphael DM, Roos L, Myovela V, *et al.* Heart diseases and echocardiography in rural Tanzania: Occurrence, characteristics, and etiologies of underappreciated cardiac pathologies. *PLoS One*2018;**13** :e0208931. doi:10.1371/journal.pone.0208931

31 Stenumgård PS, Rakotondranaivo MJ, Sletvold O, *et al.* Stroke in a resource-constrained hospital in Madagascar. *BMC Res Notes*2017;**10** :307. doi:10.1186/s13104-017-2627-4

32 Maramba A, Ncube S, Mandisodza A, *et al.* An Assessment of the Effectiveness of Warfarin Therapy Monitoring Systems on Thrombophilic Patients in Zimbabwe. *TH Open* 2018;**02** :e325–8. doi:10.1055/s-0038-1672186

33 Noubiap JJ, Nyaga UF. A review of the epidemiology of atrial fibrillation in sub-Saharan Africa. *J Cardiovasc Electrophysiol*2019;**30** :3006–16. doi:10.1111/jce.14222

34 Tegene E, Tadesse I, Markos Y, *et al.* Prevalence and risk factors for atrial fibrillation and its anticoagulant requirement in adults aged [?]40 in Jimma Town, Southwest Ethiopia: A community based cross-sectional study. *IJC Hear Vasc* 2019;**22** :199–204. doi:10.1016/j.ijcha.2019.02.003

35 Stambler B, Ngunga L. Atrial fibrillation in Sub-Saharan Africa: epidemiology, unmet needs, and treatment options. *Int J Gen Med*2015;**8** :231–42. doi:10.2147/IJGM.S84537

36 Ntep-Gweth M, Zimmermann M, Meiltz A, *et al.* Atrial fibrillation in Africa: Clinical characteristics, prognosis, and adherence to guidelines in Cameroon. *Europace*2010;**12** :482–7. doi:10.1093/europace/euq006

37 Zuhlke L, Karthikeyan G, Engel ME, *et al.* Clinical Outcomes in 3343 Children and Adults With Rheumatic Heart Disease From 14 Low- and Middle-Income Countries. *Circulation* 2016;**134** :1456–66. doi:10.1161/CIRCULATIONAHA.116.024769

38 Getachew Erkabu S, Agedie Y, Mihretu DD, *et al.* Ischemic and Hemorrhagic Stroke in Bahir Dar, Ethiopia: A Retrospective Hospital-Based Study. *J Stroke Cerebrovasc Dis*2018;**27** :1533–8. doi:10.1016/j.jstrokecerebrovasdis.2017.12.050

39 Shavadia J, Yonga G, Mwanzi S, *et al.* Clinical characteristics and outcomes of atrial fibrillation and flutter at the Aga Khan University Hospital, Nairobi. *Cardiovasc J Afr*2013;**24** :6–9. doi:10.5830/CVJA-2012-064

40 Pastakia SD, Fohl AL, Schellhase EM, *et al.* Needs assessment analysis for vitamin K antagonist anticoagulation in the resource-constrained setting of Eldoret, Kenya. *J Am Pharm Assoc*2010;**50** :723–5. doi:10.1331/JAPhA.2010.09226

41 Sidibe S, Sako M, Sacko A, *et al.* Problematique de l'anticoagulation dans la fibrillation atriale non valvulaire du sujet age. *Research* 2018;**fr5** :2618. doi:10.13070/rs.fr.5.2618

42 Moloi AH, Mall S, Engel ME, *et al.* The Health Systems Barriers and Facilitators for RHD Prevalence: An Epidemiological Meta-Analysis From Uganda and Tanzania. *Glob Heart* 2017;**12** :5–15. doi:10.1016/j.gheart.2016.12.002

43 Zuhlke LJ, Engel ME, Watkins D, *et al.* Incidence, prevalence and outcome of rheumatic heart disease in South Africa: A systematic review of contemporary studies. *Int J Cardiol*2015;**199** :375–83. doi:10.1016/j.ijcard.2015.06.145

44 Keates AK, Mocumbi AO, Ntsekhe M, *et al.* Cardiovascular disease in Africa: epidemiological profile and challenges. *Nat Rev Cardiol* 2017;**14** :273–93. doi:10.1038/nrcardio.2017.19

45 Kane A, Mirabel M, Toure K, *et al.* Echocardiographic screening for rheumatic heart disease: Age matters. *Int J Cardiol*2013;**168** :888–91. doi:10.1016/j.ijcard.2012.10.090

46 Longo-Mbenza B, Bayekula M, Ngiyulu R, *et al.* Survey of rheumatic heart disease in school children of Kinshasa town. *Int J Cardiol* 1998;**63** :287–94. doi:10.1016/S0167-5273(97)00311-2

47 Engel ME, Haileamlak A, Zuhlke L, *et al.* Prevalence of rheumatic heart disease in 4720 asymptomatic scholars from South Africa and Ethiopia. *Heart* 2015;**101** :1389–94. doi:10.1136/heartjnl-2015-307444

48 Chang AY, Nabbaale J, Okello E, *et al.* Outcomes and Care Quality Metrics for Women of Reproductive Age Living With Rheumatic Heart Disease in Uganda. *J Am Heart Assoc*2020;**9** :e015562. doi:10.1161/JAHA.119.015562

49 Danwang C, Temgoua MN, Agbor VN, *et al.* Epidemiology of venous thromboembolism in Africa: a systematic review. *J Thromb Haemost*2017;**15** :1770–81. doi:10.1111/jth.13769

50 Durand M, Sinyavskaya L, Jin YL, *et al.* Incidence of venous thromboembolism in patients living with HIV: A cohort study. *AIDS Patient Care STDS* 2019;**33** :455–8. doi:10.1089/apc.2019.0154

51 Vululi ST, Bugeza S, Zeridah M, *et al.* Prevalence of lower limb deep venous thrombosis among adult HIV positive patients attending an outpatient clinic at Mulago Hospital. *AIDS Res Ther*2018;**15** :3. doi:10.1186/s12981-018-0191-1

52 Mampuya FK, Steinberg WJ, Raubenheimer JE. Risk factors and HIV infection among patients diagnosed with deep vein thrombosis at a regional/tertiary hospital in Kimberley, South Africa. *South African Fam Pract* 2018;**60** :107–13. doi:10.1080/20786190.2018.1432135

53 Louw S, Jacobson BF, Buller H. Human Immunodeficiency Virus Infection and Acute Deep Vein Thromboses. *Clin Appl Thromb*2008;**14** :352–5. doi:10.1177/1076029607304411

54 Goldstein LN, Wu MT. A one year audit of patients with venous thromboembolism presenting to a tertiary hospital in Johannesburg, South Africa. *African J Emerg Med* 2018;**8** :12–5. doi:10.1016/j.afjem.2017.08.006

55 Awolesi D, Naidoo M, Cassimijee MH. The profile and frequency of known risk factors or comorbidities for deep vein thrombosis in an urban district hospital in KwaZulu-Natal. *South Afr J HIV Med*2016;**17** :a425. doi:10.4102/sajhivmed.v17i1.425

56 Olubanwo OO. *The profile of HIV / AIDS patients admitted with deep venous thrombosis (DVT) at Nelson Mandela Hospital in Mthatha, South Africa* . 2010.http://hdl.handle.net/10019.1/100702

57 Alshehri MF. *Risk factors for Deep Vein Thrombosis in a South African public hospital* . 2013.http://hdl.handle.net/11427/2879

58 Kamdem F, Hugo BMN, Hamadou B, *et al.* Epidemiology , Clinical Presentations and In-Hospital Mortality of Venous Thromboembolism at the Douala General Hospital : A Cross-Sectional Study in Cameroon , Sub-Saharan Africa. *World J Cardiovasc Dis*2018;**8** :123–32. doi:10.4236/wjcd.2018.82012

59 Nkoke C, Teuwafeu D, Mapina A, *et al.* A case series of venous thromboembolic disease in a semi-urban setting in Cameroon. *BMC Res Notes* 2019;**12** :40. doi:10.1186/s13104-019-4092-8

60 Abah JP, Menanga A, Ngahane BHM, *et al.* Pattern of venous thromboembolic diseases in a resources-limited setting in Cameroon.*Pan Afr Med J* 2016;**23** :236. doi:10.11604/pamj.2016.23.236.7034

61 Ogeng'o JA, Obimbo MM, Olabu BO, *et al.* Pulmonary thromboembolism in an East African tertiary referral hospital. *J Thromb Thrombolysis* 2011;**32** :386–91. doi:10.1007/s11239-011-0607-4

62 Johnson LF, May MT, Dorrington RE, *et al.* Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study. *PLOS Med*2017;**14** :e1002468. doi:10.1371/journal.pmed.1002468

63 UNAIDS. AIDSinfo. 2018.aidsinfo.unaids.org (accessed 11 May 2020).

64 Persaud N, Jiang M, Shaikh R, *et al.* Global Essential Medicines Database. 2019. doi:10.6084/m9.figshare.7814246.v1

65 Medicines Patent Pool. Patented medicines that have clinical benefits but did not meet the EML Expert Review committee's comparative cost-effectiveness criterion: Case study on novel oral anticoagulants. In: *Exploring the Expansion of the Medicines Patent Pool's Mandate to Patented Essential Medicines: A Feasibility Study of the Public Health Needs and Potential Impact* . Geneva: : Medicines Patent Pool 2015. 64–79.

66 Kibirige D, Atuhe D, Kampiire L, *et al.* Access to medicines and diagnostic tests integral in the management of diabetes mellitus and cardiovascular diseases in Uganda: Insights from the ACCODAD study.*Int J Equity Health* 2017;**16** :154. doi:10.1186/s12939-017-0651-6

67 Agyepong IA, Sewankambo N, Binagwaho A, *et al.* The path to longer and healthier lives for all Africans by 2030: the Lancet Commission on the future of health in sub-Saharan Africa. *Lancet*2017;**390** :2803–59. doi:10.1016/S0140-6736(17)31509-X

68 Dzudie A, Njume E, Abanda M, *et al.* Availability, cost and affordability of essential cardiovascular disease medicines in the south west region of Cameroon: Preliminary findings from the Cameroon science for disease study. *PLoS One* 2020;**15** :e0229307. doi:10.1371/journal.pone.0229307

69 Khuluza F, Haefele-Abah C. The availability, prices and affordability of essential medicines in Malawi: A cross-sectional study. *PLoS One* 2019;**14** :e0212125. doi:10.1371/journal.pone.0212125

70 Kanyi J, Karwa R, Pastakia SD, *et al.* Venous Thromboembolism Requiring Extended Anticoagulation Among HIV-Infected Patients in a Rural, Resource-Constrained Setting in Western Kenya. *Ann Pharmacother* 2017;**51** :380–7. doi:10.1177/1060028016686106

71 Talle M, Bonny A, Scholtz W, *et al.* Status of cardiac arrhythmia services in Africa in 2018: a PASCAR Sudden Cardiac Death Task Force report. *Cardiovasc J Afr* 2018;**29** :115–21. doi:10.5830/CVJA-2018-027

72 OpenUp. What should your medicines cost? mpr.code4sa.org (accessed 11 May 2020).

73 Bista D, Chalmers L, Bereznicki L, *et al.* Potential use of NOACs in developing countries: Pros and cons. *Eur J Clin Pharmacol* 2014;**70** :817–28. doi:10.1007/s00228-014-1693-y

74 Olsson S, Pal SN, Dodoo A. Pharmacovigilance in resource-limited countries. *Expert Rev Clin Pharmacol* 2015;**8** :449–60. doi:10.1586/17512433.2015.1053391

75 Antignac M, Diop BI, Do B, *et al.* Quality Assessment of 7 Cardiovascular Drugs in 10 Sub-Saharan Countries. *JAMA Cardiol*2017;**2** :223. doi:10.1001/jamacardio.2016.3851

76 Rudd KM, Dier JG. Comparison of two different models of anticoagulation management services with usual medical care.*Pharmacotherapy* 2010;**30** :330–8. doi:10.1592/phco.30.4.330

77 Barnes GD, Kline-Rogers E, Graves C, *et al.* Structure and function of anticoagulation clinics in the United States: an AC forum membership survey. *J Thromb Thrombolysis* 2018;**46** :7–11. doi:10.1007/s11239-018-1652-z

78 Garrison SR, Allan GM. Do specialty anticoagulation clinics really outperform primary care at INR management? *J Thromb Thrombolysis*2014;**38** :420–1. doi:10.1007/s11239-014-1113-2

79 McGuinn TL, Scherr S. Anticoagulation clinic versus a traditional warfarin management model. *Nurse Pract* 2014;**39** :40–6. doi:10.1097/01.NPR.0000451803.29453.0c

80 Wilson SJ-A, Wells PS, Kovacs MJ, *et al.* Comparing the quality of oral anticoagulant management by anticoagulation clinics and by family physicians: a randomized controlled trial. *CMAJ*2003;**169** :293–8.https://www.cmaj.ca/content/169/4/293

81 Matchar DB. Do Anticoagulation Management Services Improve Care? Implications of the Managing Anticoagulation Services Trial. *Card Electrophysiol Rev* 2003;**7** :379–81. doi:10.1023/B:CEPR.0000023144.60821.d1

82 Assefa T, Gedif T, Alemayehu B. Evaluation of Patients' Knowledge on Warfarin Therapy Among Outpatients Receiving Warfarin at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopa. *Ethiop Pharm J*2014;**30** :133–8. doi:10.4314/epj.v30i2.6

83 Nyamu D, Guantai A. Patterns of Ambulatory Anticoagulation Practices in a County Hospital in Nairobi. *Pharm J Kenya*2018;**23** :75–82.https://psk.or.ke/journals/article-25

84 Dejene F, Berihun D, Assefa T. Healthcare Professionals' Knowledge and Counseling Practice on Warfarin Therapy at Tertiary Care Teaching Hospital, Addis Ababa, Ethiopia. *Cardiovasc Pharmacol Open Access*2017;**6** :206. doi:10.4172/2329-6607.1000206

85 Tadesse TA, Alebachew M, Woldu A. Prevalence of Warfarin Drug Interaction and Warfarin Education Practice in Outpatient Setups of University Teaching Hospital: A Retrospective Chart Review and an Observational Study. *J Basic Clin Pharm*2018;**9** :262–6.https://www.jbclinpharm.org/articles/prevalence-of-warfarin-drug-interaction-and-warfarin-educationpractice-in-outpatient-setups-of-university-teaching-hospi.pdf

86 Jacobs A, Bassa F, Decloedt EH. A preliminary review of warfarin toxicity in a tertiary hospital in Cape Town, South Africa.*Cardiovasc J Afr* 2017;**28** :346–9. doi:10.5830/CVJA-2017-029

87 Abok II, Andeyaba B, Slusher T, *et al.* Point-of-care monitoring of international normalized ratio among patients with mechanical valves in Jos, North-Central, Nigeria. *Niger J Cardiol*2019;**16** :98–102. doi:10.4103/njc.njc_39_17

88 Goma F, Kalinchenko S. Atrial Fibrillation in Lusaka – Pathoaetiology, Pathophysiology and Clinical Management Challenges in Primary Care Settings. *Med J Zambia*2015;**42** :31–41.https://www.mjz.co.zm/index.php/mjz/article/view/275

89 Benade EL, Jacobson BF, Louw S, *et al.* Validation of the CoaguChek XS international normalised ratio point-of-care analyser in patients at Charlotte Maxeke Johannesburg Academic Hospital, South Africa. *South African Med J* 2016;**106** :280–3. doi:10.7196/SAMJ.2016.v106i3.9422

90 Agyepong-Yeboah AA. *Comparison of the International Normalised Ratios obtained by the CoaguChek(r) XS coagulometer and by the Haematology Laboratory for patients on warfarin therapy at Dr George Mukhari Hospital: Gauteng Province* . 2014.https://repository.smu.ac.za/handle/20.500.12308/104

91 Mbokota N, Schapkaitz E, Louw S. Verification of the qLabs international normalized ratio point-of-care device for monitoring of patients attending an anticoagulation clinic. *Int J Lab Hematol*2018;**40** :508–14. doi:10.1111/ijlh.12849

92 Kamuren Z, Kigen G, Keter A, *et al.* Characteristics of patients with thromboembolic disorders on warfarin therapy in resource limited settings. *BMC Health Serv Res* 2018;**18** :723. doi:10.1186/s12913-018-3537-4

93 Nyandigisi EM. *Comparative Effectiveness and Cost Analysis of an Anticoagulation Clinic Versus Laboratory Based Practice in Kenyan Tertiary Referral Hospitals* . 2018.http://erepository.uonbi.ac.ke/handle/11295/104521

94 Canadian Agency for Drugs and Technologies in Health. Point-of-Care Testing of International Normalized Ratio for Patients on Oral Anticoagulant Therapy: Systematic Review and Economic Analysis. Ottawa: : The Agency 2014. http://www.cadth.ca/media/pdf/OP0515_POC INR_Science_Report.pdf

95 Anakwue R, Nwagha T, Ukpabi O, *et al.* A Survey of Clinicians Practice Patterns in Anticoagulation Therapy & Prophylaxis in Nigeria.*Haematol Int J* 2018;**2** :1–8. doi:10.23880/HIJ-16000125

96 Ministry of Health Ghana. *Standard Treatment Guidelines* . Sixth edit. Accra: : Ghana National Drugs Programme 2010.

97 Ministry of Health and Social Services Namibia. *Namibia Standard Treatment Guidelines* . First edit. Windhoek: : Ministry of Health and Social Services 2011.

98 Food Medicine and Health Care Administration and Control Authority Ethiopia. *Standard Treatment Guidelines for General Hospitals* . Third edit. Addis Ababa: : Food Medicine and Health Care Administration and Control Authority 2014.

99 Ministry of Health Uganda. *Uganda Clinical Guidelines 2016. National Guidelines for Mangaement of Common Conditions* . Kampala: : Ministry of Health 2016.

100 Division of Non-Communicable Diseases Ministry of Health Kenya.*Kenya National Guidelines for Cardiovascular Diseases Management* . Nairobi: : Ministry of Health 2018.

101 National Department of Health South Africa. *Standard Treatment Guidelines And Essential Medicines List for South Africa: Hospital Level, Adults* . 5th edit. Pretoria: : National Department of Health 2019.

102 Van Spall HGC, Wallentin L, Yusuf S, *et al.* Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centers and countries: An analysis of patients receiving warfarin in the RE-LY trial.*Circulation* 2012;**126** :2309–16. doi:10.1161/CIRCULATIONAHA.112.101808

103 Hill SW, Varker AS, Karlage K, *et al.* Analysis of drug content and weight uniformity for half-tablets of 6 commonly split medications. *J Manag Care Pharm* 2009;**15** :253–61. doi:10.18553/jmcp.2009.15.3.253

104 Asiimwe IG, Zhang EJ, Osanlou R, *et al.* Genetic Factors Influencing Warfarin Dose in Black-African Patients: A Systematic Review and Meta-Analysis. *Clin Pharmacol Ther*2020;**107** :1420–33. doi:10.1002/cpt.1755

105 Teklay G, Shiferaw N, Legesse B, *et al.* Drug-drug interactions and risk of bleeding among inpatients on warfarin therapy: A prospective observational study. *Thromb J* 2014;**12** :20. doi:10.1186/1477-9560-12-20

106 Maina MW, Pastakia SD, Manji I, *et al.* Describing the profile of patients on concurrent rifampin and warfarin therapy in Western Kenya: A case series. *Drugs R D* 2013;**13** :191–7. doi:10.1007/s40268-013-0023-7

107 Sekaggya C, Nalwanga D, Von Braun A, *et al.* Challenges in achieving a target international normalized ratio for deep vein thrombosis among HIV-infected patients with tuberculosis: A case series.*BMC Hematol* 2016;**16** :16. doi:10.1186/s12878-016-0056-6

108 Tarus NK, Pau AK, Sereti I, *et al.* Challenges in Management of Warfarin Anti-Coagulation in Advanced HIV/AIDS Patients with Venous Thrombotic Events - A Case Series from a Research Clinic in Rural Kericho, Kenya. *East Afr Med J*2013;**90** :207–13.https://www.ajol.info/index.php/eamj/article/view/108234

109 Ahmed SM, Nordeng H, Sundby J, *et al.* The use of medicinal plants by pregnant women in Africa: A systematic review. *J Ethnopharmacol* 2018;**224** :297–313. doi:10.1016/j.jep.2018.05.032

110 Liwa AC, Smart LR, Frumkin A, *et al.* Traditional Herbal Medicine Use Among Hypertensive Patients in Sub-Saharan Africa: A Systematic Review. *Curr Hypertens Rep* 2014;**16** :437. doi:10.1007/s11906-014-0437-9

111 Cordier W, Steenkamp V. Herbal remedies affecting coagulation: A review. *Pharm Biol* 2012;**50** :443–52. doi:10.3109/13880209.2011.611145

112 Awortwe C, Makiwane M, Reuter H, *et al.* Critical evaluation of causality assessment of herb–drug interactions in patients. *Br J Clin Pharmacol* 2018;**84** :679–93. doi:10.1111/bcp.13490

113 Mariita K, Nyamu D, Maina C, *et al.* Patient Associated Factors that Affect Adherence to Warfarin Therapy in a Tertiary Referral Hospital in Kenya. *East Cent African J Pharm Sci*2015;**18** :43–50.https://www.ajol.info/index.php/ecajps/article/view/177867

114 Chang AY, Nabbaale J, Nalubwama H, *et al.* Motivations of women in Uganda living with rheumatic heart disease: A mixed methods study of experiences in stigma, childbearing, anticoagulation, and contraception. *PLoS One* 2018;**13** :e0194030. doi:10.1371/journal.pone.0194030

115 Morisky DE, Ang A, Krousel-Wood M, *et al.* Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens* 2008;**10** :348–54. doi:10.1111/j.1751-7176.2008.07572.x

116 Iqbal S. *Effect of a Designed Warfarin Based Education Program on Patients' Knowledge and Anticoagulation Control Among Adult Outpatients Attending Clinics at Kenyatta National Hospital* . 2017.http://erepository.uonbi.ac.ke/handle/11295/103355

117 Eltayeb TYM, Mohamed MS, Elbur AI, *et al.* Satisfaction with and adherence to warfarin treatment: A cross-sectional study among Sudanese patients. *J Saudi Hear Assoc* 2017;**29** :169–75. doi:10.1016/j.jsha.2016.10.007

118 Morisky DE, Green LW, Levine DM. Concurrent and Predictive Validity of a Self-reported Measure of Medication Adherence. *Med Care*1986;**24** :67–74. doi:10.1097/00005650-198601000-00007

119 Dwamena JA. *Knowledge Level and Anticoagulation Control Among Patient on Warfarin Therapy at the National Cardiothoracic Center, Korle Bu Teaching Hospital* .

2012.http://ugspace.ug.edu.gh/handle/123456789/23702%09

120 Gregersen NE. *The implications to women of childbearing age taking Warfarin Anticoagulation* . 2006.http://hdl.handle.net/10539/1838

121 Taylor FC, Ramsay ME, Tan G, *et al.* Evaluation of patients' knowledge about anticoagulant treatment. *Qual Heal Care*1994;**3** :79–85. doi:10.1136/qshc.3.2.79

122 Briggs AL, Jackson TR, Bruce S, *et al.* The development and performance validation of a tool to assess patient anticoagulation knowledge. *Res Soc Adm Pharm* 2005;**1** :40–59. doi:10.1016/j.sapharm.2004.12.002

123 Zeolla MM, Brodeur MR, Dominelli A, *et al.* Development and validation of an instrument to determine patient knowledge: The oral anticoagulation knowledge test. *Ann Pharmacother*2006;**40** :633–8. doi:10.1345/aph.1G562

124 Hutheram K. *Investigating Patients' Knowledge and Use of the Patient Information Leaflet Regarding Their Warfarin Therapy* . 2016.http://hdl.handle.net/10413/17693

125 Samadoulougou A, Temoua Naibe D, Mandi G, *et al.* Evaluation of the level of knowledge of patients on treatment with vitamin K antagonists in Ouagadougou cardiology department. *Pan Afr Med J*2014;**19** :286. doi:10.11604/pamj.2014.19.286.5411

126 Janoly-Dumenil A, Bourne C, Loiseau K, *et al.* Traitement anticoagulant oral - Evaluation des connaissances des patients hospitalises en services de medecine physique et readaptation. *Ann Phys Rehabil Med* 2011;**54** :172–80. doi:10.1016/j.rehab.2011.02.007

127 Ng SS, Lai NM, Nathisuwan S, *et al.* Comparative efficacy and safety of warfarin care bundles and novel oral anticoagulants in patients with atrial fibrillation: a systematic review and network meta-analysis. *Sci Rep* 2020;**10** :662. doi:10.1038/s41598-019-57370-2

128 Rabkin M, Melaku Z, Bruce K, *et al.* Strengthening Health Systems for Chronic Care: Leveraging HIV Programs to Support Diabetes Services in Ethiopia and Swaziland. *J Trop Med*2012;**2012** :137460. doi:10.1155/2012/137460

129 Yiu A, Bajorek B. Patient-focused interventions to support vulnerable people using oral anticoagulants: a narrative review.*Ther Adv Drug Saf* 2019;**10** :1–27. doi:10.1177/2042098619847423

130 Kanters S, Park JJH, Chan K, *et al.* Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV* 2017;**4** :e31–40. doi:10.1016/S2352-3018(16)30206-5

131 Rusingiza EK, El-Khatib Z, Hedt-Gauthier B, *et al.* Outcomes for patients with rheumatic heart disease after cardiac surgery followed at rural district hospitals in Rwanda. *Heart*2018;**104** :1707–13. doi:10.1136/heartjnl-2017-312644

132 Wiggins BS, Dixon DL, Neyens RR, *et al.* Select Drug-Drug Interactions With Direct Oral Anticoagulants: JACC Review Topic of the Week. *J Am Coll Cardiol* 2020;**75** :1341–50. doi:10.1016/j.jacc.2019.12.068

Table 1. Observational studies from sub-Saharan Africa which measured time in therapeutic range (TTR) or proportion of INR results in therapeutic range (PTR) among patients on anticoagulation.

Study, publication year	**Setting**
Makubi,[6] 2008	Dar es Salaam, Tanzania. National referral hospital.
Manji,[7] 2011	Eldoret, Kenya. Teaching hospital.
Menanga,[8] 2015	Yaoundé, Cameroon. A general and a central hospital.
Daba,[9] 2016	Addis Ababa, Ethiopia. Teaching hospital.
Mariita,[10] 2016	Nairobi, Kenya. Teaching hospital.
Sadhabiriss,[11] 2016	Durban, South Africa. District-level hospital.
Sonuga,[12] 2016	Cape Town, South Africa. District hospital.

Study, publication year	Setting
Ahmed,[13] 2017	Khartoum, Sudan. Specialist hospital.
Fenta,[14] 2017	Addis Ababa, Ethiopia. Teaching hospital.
Nyamu,[15] 2017	Nairobi, Kenya. Teaching hospital.
Coulibaly,[16] 2018	Abidjan, Côte d'Ivoire. Specialist hospital.
Ebrahim,[17] 2018	Cape Town, South Africa. A specialist hospital and a community health centre.
Mwita,[18] 2018	Gaborone, Botswana. Tertiary hospital.
Jonkman,[19] 2019	Windhoek, Namibia. Central hospital.
Karuri,[20] 2019	Nairobi, Kenya. Teaching hospital.
Botsile,[21] 2020	Gaborone, Botswana. Tertiary hospital.
Semakula,[22] 2020	Kampala, Uganda & Cape Town, South Africa. A primary level health centre and four second

ACC: anticoagulation clinic; AF: atrial fibrillation; PTR: proportion of INR results in therapeutic range; TTR: time in therapeutic range; VKA: vitamin K antagonist; VTE: venous thromboembolism.

Table 2. Studies from sub-Saharan Africa reporting the prevalence of HIV and tuberculosis among patients presenting to hospitals for venous thromboembolism

Study	Setting	Population HIV
Mampuya[52]	Regional / tertiary hospital, Kimberley, Northern Cape, South Africa, 2010-2014.	11.0%
Louw[53]	Tertiary hospital, Johannesburg, Gauteng, South Africa, date NR.	16.9%
Goldstein[54]	Tertiary hospital emergency centre, Johannesburg, Gauteng, South Africa, 2012-2013.	17.8%
Awolesi[55]	Urban district hospital, KwaZulu-Natal, South Africa, 2013.	27.0%
Olubanwo[56]	Tertiary hospital, Mthatha, Eastern Cape, South Africa, 2010.	18.0%
Alshehri[57]	District hospital, Cape Town, Western Cape, South Africa, 2008-2011.	8.9%
Kamdem[58]	Tertiary urban hospital, Douala, Cameroon, 2008-2016.	3.6%
Nkoke[59]	Semi-urban regional hospital, Buea, Cameroon, 2016-2017.	3.6%
Abah[60]	Semi-urban military hospital, Bamenda, Cameroon, 2010-2013.	3.6%
Ogeng'o[61]	National referral hospital, Nairobi, Kenya, date NR.	4.7%

[a] HIV prevalence among adults 15 to 49 years old. For South Africa, these are provincial estimates from the Thembisa model[62] for the final year of study data collection (or publication, if not reported). For other countries, these are 2018 national estimates by UNAIDS.[63]

Table 3. Examples of warfarin dose initiation and dose adjustment guidelines for venous thromboembolism by SSA countries' departments or ministries of health

Guideline	Warfarin dose initiation guideline	Warfarin dose adjustment guideline
Ghana Standard Treatment Guidelines 2010[96]	"Warfarin, oral, adults: 10 mg daily at 6pm for 2 days, then 5 mg daily"	"regular dose adjustment and monitoring of INR until target of 2.0 and 3.0 is attained"
Namibia Standard Treatment Guidelines 2011[97]	"Warfarin: 5 to 10 mg orally; start at same time as heparin"	"adjust dose according to INR"
Ethiopia Standard Treatment Guidelines for General Hospitals 2014[98]	"Warfarin (starting simultaneously with heparin), 5 mg orally, daily"	"dose adjusted to achieve target INR of 2.0 to 3.0"

Guideline	Warfarin dose initiation guideline	Warfarin dose adjustment guideline
Uganda Clinical Guidelines. National Guidelines for Management of Common Conditions 2016[99]	"... plus warfarin 5mg single dose given in the evening, commencing on the same day as heparin"	"Maintenance dose 2.5 to 7.5 mg single dose daily, adjusted according to the INR 2 to 3"
Kenya National Guidelines for Cardiovascular Diseases Management 2018[100]	"Recommended starting dose: 5 mg orally once a day"	"Typical maintenance dose: 2 to 10 mg orally once a day. Dosage must be individualized according to the patient's INR"
Standard Treatment Guidelines and Essential Medicines List for South Africa, Hospital Level, Adults 2019[101]	*Day 1*: 5 mg daily (2.5 mg daily for high sensitivity) *2 to 3 days after initiation*: 5-7.5 mg/d if INR < 1.5; 2.5-5 mg/d if INR 1.5 to 1.9; 2.5 mg/d if INR 2.0 to 2.5; hold warfarin if INR > 2.5 *2 to 3 days after last INR check:* 7.5-10 mg/d if INR < 1.5; 5-10 mg/d if INR 1.5 to 1.9; 2.5-5 mg/d if INR 2.0 to 3.0; hold warfarin if INR $>$ 3	Increase weekly dose by 10% if INR < 1.5; increase weekly dose by 5% if INR 1.5 to 1.9; no change to warfarin dose if INR 2.0 to 3.0; decrease weekly dose by 5% if INR 3.1 to 4.0; decrease weekly dose by 10% if INR 4.1 to 5.0; decrease weekly dose by 20% if INR 5.1 to 9.0

Table 4. Sub-Saharan African studies of patients' self-reported adherence to anticoagulation.

Study	Setting, sample
Chalachew[29]	Addis Ababa, Ethiopia, 2019. Children and young adults (11 to 25 years) with prosthetic valves on anticoa
Mariita[113]	Nairobi, Kenya, 2015. Consecutive sample at cardiac, cardiothoracic, and hemato-oncology clinics of a teac
Iqbal[116]	Nairobi, Kenya, 2017. Convenience sample at cardiac, cardiothoracic, hemato-oncology, and DVT clinics of
Eltayeb[117]	Khartoum, Sudan, 2017. Convenience sample at cardiothoracic clinic of a teaching hospital

Table 5. Sub-Saharan African studies of patients' knowledge about anticoagulation.

Study	Setting, sample
Dwamena[119]	Accra, Ghana, 2012. Systematic sample of outpatients at anticoagulation clinic of a teaching hospita
Assefa[82]	Addis Ababa, Ethiopia, 2014. Outpatients on warfarin at teaching hospital.
Mariita[10]	Nairobi, Kenya, 2016. Consecutive sample at cardiac, cardiothoracic, and hemato-oncology clinics of
Iqbal[116]	Nairobi, Kenya, 2017. Convenience sample at cardiac, cardiothoracic, hemato-oncology, and DVT cli
Hutheram[124]	Gauteng, South Africa, 2016. Convenience sample at ten private sector INR clinics attached to a pri
Samadoulougou[125]	Ouagadougou, Burkina Faso, 2014. Convenience sample of patients in the cardiology clinic of a univ
Maramba[32]	Harare, Zimbabwe, 2018. Convenience sample of outpatients with thrombophilia on long-term warfar
Gregersen[120]	Johannesburg, South Africa, 2006. Convenience sample of women of childbearing age with valvular h

Figure 1. Example observational studies from sub-Saharan Africa which described resource limitations

Burkina Faso, 2016 – 2019[25,26]
INR monitoring only available in the largest two cities.

Nigeria, 2014[27]
There are no anticoagulation clinics in the country.

Zambia, 2019[28]
Rural referral hospital serving population of 1.5 million people had no INR monitoring available.

Botswana, 2018 – 2020[18,21]
Largest tertiary hospital in the country had anticoagulation clinic first established in 2016/2017.

Ethiopia, 2019[29]
A quarter of patients with prosthetic heart valves live more than 150 km from the cardiac clinic.

Tanzania, 2018[30]
Rural referral hospital had echocardiography available but not INR monitoring.

Madagascar, 2017[31]
Regional capital city with population of 250,000 people served by four hospitals had no laboratory which performed INR.

Zimbabwe, 2018[32]
There are no anticoagulation clinics in the country.