Anticoagulation in sub-Saharan Africa: Are direct oral anticoagulants the answer? A review of lessons learnt from warfarin

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INTRODUCTION

Medical conditions that require anticoagulation are important causes of morbidity and mortality worldwide, but are often unrecognized or under-treated in low- and middle-income countries (LMIC) including sub-Saharan Africa (SSA).1 Venous thromboembolism (VTE), presenting clinically as deep venous thrombosis (DVT) and/or pulmonary embolism is a key example.2 The prevalence of DVT varies between 2.4 and 9.6% in postoperative patients, and between 380 and 448 per 100 000 births per year in pregnant and postpartum women in SSA.1,2 Many hospitalized patients are at risk of VTE, but a multinational cross-sectional study of over 1500 hospitalized patients in SSA found that while 50.4% were at risk for VTE, only 51.5% of these received recommended forms of prophylaxis.3 The mortality of patients diagnosed with pulmonary embolism is alarmingly high ranging from 40 to 69.5%.1

Life expectancy is increasing across SSA4 due to reduced childhood mortality5 and improved control of infectious diseases, especially HIV.6 This increasing life expectancy is associated with increased prevalence of cardiovascular diseases such as hypertension and atrial fibrillation (AF). In addition, rheumatic heart disease (RHD), a leading cause of heart failure in SSA,7 is present in 12–66% of hospitalized patients presenting with AF in this region.8 The rise in such cardiovascular diseases has

Warfarin has existed for >7 decades and has been the anticoagulant of choice for many thromboembolic disorders. The recent introduction of direct-acting oral anticoagulants (DOACs) has, however, caused a shift in preference by healthcare professionals all over the world. DOACs have been found to be at least as effective as warfarin in prevention of stroke in patients with atrial fibrillation and in treatment of venous thromboembolism. In sub-Saharan Africa, however, the widespread use of DOACs has been hampered mainly by their higher acquisition costs. As the drugs come off patent, their use in sub-Saharan Africa is likely to increase. However, very few trials have been conducted in African settings, and safety concerns will need to be addressed with further study before widespread adoption into clinical practice.

KEYWORDS
cardiovascular disease, direct oral anticoagulants, sub-Saharan Africa, warfarin
created an increased requirement for the use of anticoagulant therapy.

Warfarin, a vitamin K antagonist (VKA) has existed for >70 years and is the mainstay of anticoagulation therapy in SSA. The direct-acting oral anticoagulants (DOACs) have been shown to be at least as effective as warfarin for treatment of VTE and for stroke prevention in atrial fibrillation and are already widely used in high-income countries. DOAC use is increasing in LMIC and is likely to increase further as the drugs come off patent. However, there remain unanswered questions regarding their use and situations where warfarin remains useful. This review aims to examine the role of DOACs in SSA by applying lessons learnt with warfarin use.

1.1 Bleeding and reversal

The clinical pharmacology of warfarin and DOACs (including factor Xa inhibitors apixaban, edoxaban and rivaroxaban, and the direct thrombin inhibitor dabigatran) has been extensively described elsewhere. We focus on specific challenges of anticoagulants resulting from their pharmacological properties, with reference to the SSA context. Firstly, any clinical benefit of preventing thrombosis must be measured against the risk of bleeding, which can be challenging in LMIC, where laboratory and clinical services are inadequate. The lack of validated bleeding risk prediction tools leaves patients starting anticoagulation at risk of bleeding. A cross-sectional study in South Africa found warfarin among the top 4 causes of adverse drug reactions and the leading cause of preventable drug-related haemorrhage. Unfortunately, there is limited knowledge on the rates of bleeding or risk profiles among patients in SSA taking warfarin or DOACs. In large international phase III RCTs, major bleeding rates with DOACs have been generally lower compared to warfarin but patients on dabigatran and rivaroxaban had higher rates of major gastrointestinal bleeding compared to those receiving warfarin. For warfarin reversal, vitamin K is effective, affordable and readily available in LMIC. Specific reversal agents for DOACs have not existed until recently and are not yet available on the market in SSA. In addition, their expense is prohibitive for routine use even in high-income countries. Concerns about the lack of reversal agents may limit DOAC prescribing, especially in SSA where plasma derived medicinal products that are useful in clinical management of bleeding such as prothrombin complex concentrate and fresh frozen plasma, are expensive and scarce.

1.2 Drug monitoring

Warfarin dose can be adjusted using standardized dosing schedules to achieve the desired International Normalized Ratio (INR) target, with the success of these adjustments expressed by the time in therapeutic range (TTR). Higher TTR is generally associated with fewer bleeding events and lower mortality. Studies conducted in the operational context in SSA show that the median TTR is low, ranging between 29 and 47%. This contrasts with clinical trial participants on the warfarin arm of studies comparing warfarin with DOACS who achieved TTRs between 58-69%, which is closer to that seen in high income countries where specialist clinics, more frequent monitoring including patient self-testing, guidelines and the use of clinical dosing algorithms may account for better control. The inadequate patient knowledge and adherence counselling leading to low TTR may also lead to suboptimal treatment with DOACs. INR monitoring can aid assessment of warfarin adherence and may actually improve this by increasing frequency of clinical interactions. Assessing DOAC adherence relies solely on adherence assessment tools that are prone to error. Few studies explore factors associated with adherence to oral anticoagulants in SSA. However, research among heart failure patients indicates that medication adherence is a major concern, often resulting from poor patient treatment knowledge. Studies from high-income countries comparing adherence to warfarin and DOACs show varying results. Factors influencing anticoagulant adherence in SSA need to be explored especially for DOACs where drug monitoring may not be feasible.

It may be necessary to perform DOAC monitoring to assist in clinical decision-making for patients with extremes of body weight,
acute renal injury, recurrent thrombosis and drug–drug interactions. Other patient groups that are not routinely included in clinical trials of DOACs and yet are frequently encountered in SSA, such as those on antiretroviral therapy for HIV or those on rifampicin for tuberculosis may also be at risk of either bleeding or thrombosis due to exaggerated or inadequate effects resulting from drug–drug interactions with DOACs. In addition, Asian race has been shown to have a significant impact on clearance of dabigatran and modest non-clinically significant effect on apixaban clearance.

We do not know the impact of the African race on the pharmacokinetics of DOACs. Therefore, having a measure of pharmacodynamic response (INR in the case of warfarin) is important. Whereas DOACs may prolong prothrombin time, INR and activated partial thromboplastin time, changes observed in these at therapeutic doses are highly variable and correlate poorly with DOAC effect. Therefore specific drug anti-factor Xa assays using reagents and reference ranges that are specific to the SSA population should be established for DOAC monitoring to inform dosage adjustment.

2 | ANTICOAGULATION IN AF AND VALVULAR HEART DISEASE

Few studies have assessed the prevalence of AF in SSA, reporting prevalence ranging from 0.3 to 0.7% in rural communities to 4% in urban communities. It is highest in patients with known cardiac disease, more frequently due to valvular heart disease (VHD), often resulting from RHD, in SSA than in Europe or North America. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) AF registry, which included 1137 patients from 9 countries in SSA, 21.5% of these patients had RHD compared to 2.2% of patients from North America and 1.5% among those enrolled from western Europe. Hospital based studies have reported coexisting VHD in 10–53% of patients with AF in SSA.

The mortality rate of patients with AF, particularly valvular, ranges from 10 to 40% after 1 year. This has been attributed to late presentation of patients with advanced disease and suboptimal use of oral anticoagulant therapy compounded by suboptimal anticoagulation control in patients who are taking warfarin. Fortunately, subgroup analyses of the trial participants of the 4 major Phase III trials comparing warfarin to DOACs found that DOACs can be safely used in patients with forms of VHD such as aortic stenosis, aortic regurgitation and mitral regurgitation. DOACs may therefore prove to be as effective as warfarin in patients with VHD, which will positively impact RHD care in SSA. Consequently, the efficacy of rivaroxaban is being compared to warfarin in patients with RHD and AF at high risk of stroke in the INVICTUS trial, an international, multicentre, randomized open-label trial that has enrolled over 25% of its participants (1150) from 14 SSA countries (Table 1).

Although still scarce in many countries in this region, heart valve replacement surgery accounts for some need for long term anticoagulation in SSA. In these patients, warfarin is superior to DOACs since the mechanism by which valve components induce thrombin generation would require much higher DOAC doses than those currently recommended.

3 | ANTICOAGULATION IN PREGNANCY

Anticoagulation in pregnancy is a particular challenge in LMIC. All available oral anticoagulants may cause maternal and fetal complications. Most guidelines recommend use of heparin during pregnancy, since lack of transplacental transfer eliminates the possibility of direct drug-related embroyopathy. However, heparins are prohibitively expensive in most of SSA, where patients must meet their healthcare expenses. An example is Uganda, where a vial of enoxaparin 80 mg costs about 17 USD or up to 500 USD for a month’s supply. With an average monthly household income of about 115 USD, this is beyond what many Ugandans can afford. It is not uncommon for women in SSA on long-term oral anticoagulation to continue using warfarin even during pregnancy. Warfarin is an effective anticoagulant even in pregnancy but there remains a risk of foetal complications if used in first trimester. Since warfarin-related foetal complications are dose related, use of low doses (<5 mg) to attain a target INR 1.5–2.5 in pregnancy has been associated with better pregnancy outcomes with reduced foetal embryopathy and mortality. This may benefit pregnant patients in SSA on long-term prophylaxis due to recurrent DVT and those with mechanical heart valves who are unable to afford heparin.

Currently, DOACs are not licensed for use in pregnancy. Animal studies in both rats and rabbits have demonstrated fetotoxic effects of dabigatran and edoxaban. Furthermore, DOACs have been reported to be excreted in breast milk. Case reports of mothers taking rivaroxaban at standard doses indicate excretion into breast milk, albeit at low relative infant doses with potentially higher exposure for apixaban. Conversely, warfarin was undetectable in the breast milk and infant plasma in small studies where mothers received a range of doses. It is yet to be established if presence of DOACs in breast milk has implications for the nursing infant. This warrants further study in SSA where up to 96% of infants are breastfed.

4 | COST OF WARFARIN VS. DOACS

Treatment costs must consider direct costs such as the cost of medication, expenses associated with monitoring, admissions due to complications and additional treatments to achieve effective INR. Additionally, indirect costs such as lost employment time and productivity associated with anticoagulation should be estimated. The biggest hindrance to using DOACs especially in LMIC has been inaccessibility and high cost of drug compared to vitamin K antagonists. In Uganda, a 5 mg warfarin tablet costs approximately 0.2 USD, significantly lower than the 2–4 USD that would be required to purchase a 15 mg tablet of rivaroxaban. Cost of monitoring varies across the region and adds to the overall cost of anticoagulation treatment incurred by patients. For instance, an INR test in Uganda costs 5 USD
### TABLE 1  Phase III randomized clinical trials comparing warfarin to direct-acting oral anticoagulants in AF in SSA

| Author, Year Study, Short Title | Trial objective | Participating SSA countries | Total enrolment and ethnicity of sample population | Key exclusion criteria |
|--------------------------------|----------------|----------------------------|-----------------------------------------------|-----------------------|
| Connolly, 2009 RE-LY           | To compare the use of dabigatran, at doses of 110 mg twice daily and 150 mg twice daily, with warfarin. | South Africa 18 113 participants White:70% Asian:15.9% Black:1% Other:13.1% | -History of heart valve disorder (prosthetic valve or haemodynamically relevant valve disease) -Severe renal impairment (estimated CrCl ≤ 30 mL/min) -Pregnant women and women of childbearing potential who refuse to use medically acceptable form of contraception |
| Patel, 2011 ROCKET-AF          | To compare once-daily oral rivaroxaban with dose-adjusted warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation who were at moderate-to-high risk for stroke | South Africa 14 264 participants Ethnicity not described | -Haemodynamically significant mitral valve stenosis -Prosthetic heart valve patients -Pregnancy or breastfeeding -Known HIV infection at screening Calculated CrCl <30 mL/min |
| Granger, 2011 ARISTOTLE        | To compare apixaban with warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation and at least 1 additional risk factor for stroke | South Africa 18 201 participants White:82.6% Asian:14.5% Black:1.2% Indian: 0.3% Other:1.4% | -Clinically significant (moderate or severe) mitral stenosis -Severe renal insufficiency serum creatinine >2.5 mg/dL or a calculated CrCl <25 mL/min -Pregnant or breastfeeding women and women of child-bearing potential unwilling or unable to use an acceptable method to avoid pregnancy |
| Giugliano, 2013 ENGAGE AF-TIMI 48 | To compare 2 dose regimens of once-daily edoxaban with warfarin in patients with atrial fibrillation who were at moderate-to-high risk for stroke. | South Africa 21 105 participants White:80.9% Asian:13.8% Black:1.3% Notreported:4.0% | -Subjects with moderate to severe mitral stenosis, mechanical heart valves (subjects with bioprosthetic valves and or valve repair were included) -Calculated CrCl <30 mL/min Subjects receiving antiretroviral therapy for HIV -Females of childbearing potential |
| Karthikeyan, 2020 INVICTUS      | To determine the safety and efficacy of rivaroxaban compared to vitamin K antagonists for stroke prevention in RHD and AF | Botswana, Cameroon, Ethiopia, Kenya, Malawi, Mozambique, Nigeria, Rwanda, South Africa, Sudan, Tanzania, Uganda, Zambia, Zimbabwe 4565 participants South Asian:17.3% Chinese:5.1% Other Asian:17.6% Arab:17.1% Black African:25.3% Latin American:7.6% Other:10.1% | -Presence of a mechanical valve -Severe renal insufficiency (eGFR < 15 mL/min) -Pregnant women and women of child-bearing potential not using effective contraception |

AF: atrial fibrillation; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; HIV: human immunodeficiency virus; RHD: rheumatic heart disease; SSA: sub-Saharan Africa.
in urban hospitals\textsuperscript{27} but may be higher in private laboratories in rural settings. Importantly, INR testing services may be offered free of charge to patients in public hospitals in some countries including South Africa, whereas they are paid for by the patient in countries such as Uganda\textsuperscript{27} where government health insurance schemes do not yet exist. The cost effectiveness of DOACs, which are now included on the World Health Organization Essential Medicines List\textsuperscript{71} must be explored across SSA if roll-out to public health facilities is proposed.

5 | CONCLUSION

Whilst noting the challenges, warfarin will remain the drug of choice for oral anticoagulation in SSA for the time being as DOACs are still expensive and largely inaccessible. Specific research on DOACs in SSA is required to inform guidelines for their safe and cost-effective use.

CONTRIBUTORS

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