Anticoagulation in sub-Saharan Africa: Are Direct Oral Anticoagulants the answer? A review of lessons learnt from warfarin

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Abstract:

Warfarin has existed for more than seven 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.

Introduction

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

SSA is experiencing an increase in life expectancy[4] due to a reduction in childhood mortality[5] and improved control of infectious diseases, especially HIV[6], which ravaged this region for several years. 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 to 66% of hospitalized patients presenting with AF in this region[8]. The rise in such cardiovascular diseases has created an increased requirement for the use of anticoagulant therapy.

Warfarin, a vitamin K antagonist (VKA) has existed for more than 70 years and is the mainstay of anticoagulation therapy in SSA. The alternative agents, commonly referred to as Direct-Acting Oral Anticoagulants (DOACs) have been shown to be at least as effective as warfarin for treatment of VTE[9] and for stroke prevention in atrial fibrillation[10] and are already widely used in Western countries. DOACs are recommended as first choice in eligible patients with acute VTE[11] and are preferred to warfarin because they have more predictable pharmacokinetics allowing fixed dosing which in most cases does not require therapeutic drug monitoring. Additionally, DOACs have fewer drug-drug interactions (DDIs) than warfarin. DOAC use is increasing in developing countries and is likely to increase further as the drugs come off patent. However, there are several unanswered questions regarding the use of DOACs where warfarin may continue to remain useful. The purpose of this review is to examine the role of DOACs in SSA by applying lessons learnt with warfarin use.

Clinical Pharmacology of Warfarin Versus DOACs

Warfarin is an oral coumarin derivative that interferes with synthesis of vitamin K dependent clotting factors through competitive inhibition of Vitamin K epoxide reductase complex 1 (VKORC1)[12]. Warfarin depletes vitamin K reserves thereby decreasing the synthesis of active clotting factors. For this reason, large changes in dietary intake of vitamin K can affect the anticoagulant effect of warfarin[13]. The DOACs, which include factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) and the direct thrombin inhibitor dabigatran, are generally unaffected by food.

Due to the half-life of circulating clotting factors, the onset of action of warfarin occurs between 36-48 hours after initiation of therapy[12]. Initiation of warfarin therapy may therefore require concurrent administration of the faster-acting anticoagulant heparin until adequate anticoagulation with warfarin has been achieved. DOACs on the other hand begin to work within a few hours following administration due to their direct inhibitory actions. With a half-life ranging from 20 to 60 hours, the duration of action of warfarin lasts from 2-5 days[14]. Warfarin must therefore be stopped for a longer period prior to performing invasive surgical procedures to prevent intraoperative bleeding complications. DOACs have shorter half-lives (Table 1) which requires stricter adherence by patients to ensure adequate continuous anticoagulation cover. This may be of concern in low income settings where poor patient adherence to anticoagulants is still a challenge[15].

{Table 1 here}

The more potent warfarin enantiomer, S-warfarin, is metabolized by CYP2C9 while R-warfarin is metabolized by a range of P450 enzymes including CYP1A2, CYP2C19 and CYP3A4[16]. Warfarin therefore interacts with a number of other drugs that either induce or inhibit these enzymes. Apixaban, rivaroxaban and edoxaban are also partly metabolized by CYP3A4 and are prone to drug-drug interactions with strong cytochrome P450 inducers and inhibitors as well as P-glycoprotein (P-gp) modulators[17]. Dabigatran does not undergo metabolism by P450 enzymes but its prodrug dabigatran etexilate is a substrate for P-gp[18]. Härtter and colleagues showed a decrease in dabigatran exposure of up to two-thirds when given together with rifampicin, a strong inducer of intestinal and hepatic P-gp[19]. Similar effects of rifampicin on apixaban[20] and edoxaban[21] have been reported. In contrast, P-gp inhibitors clarithromycin and cobicistat have been demonstrated to significantly increase DOAC pharmacokinetic parameters. When co-administered with clarithromycin, the C_{max} of dabigatran and rivaroxaban increased by 80% ($p=0.0007$) and 92% ($p < 0.0001$) respectively compared to single administration of either DOAC[22]. These drug-drug interactions have clinical implications as they increase the risk of major bleeding in patients taking warfarin[23] or DOACs[17] [24], and therefore concurrent use is either contraindicated or needs to proceed with enhanced monitoring.

In addition to drug-drug interactions, genetic polymorphisms in CYP2C9, VKORC1 and CYP4F2 genes may affect individual patient warfarin dosing requirements[25, 26]. Furthermore, the allelic variants in these genes which affect dose requirements may differ between different ethnic groups[27]. Genetic polymorphisms may also have an effect on DOAC pharmacokinetics, but the overall effect is much less than that observed with warfarin. A Genome Wide Association Study (GWAS) performed in 1694 participants of white European ancestry in the RE-LY trial found that the rs2244613 Single Nucleotide Polymorphism (SNP) in the esterase gene, CES1, was associated with decreased trough concentrations of dabigatran and decreased risk of bleeding while the CES1 SNP rs8192935 and ABCB1 SNP rs4148738 were associated with peak concentrations but not with clinical outcome[28]. There is a paucity of data on clinically important genetic polymorphisms that influence metabolism and response to factor Xa inhibitors[29] in all patient groups including those from SSA. However, it seems that pharmacogenetic factors are likely to account for a much smaller degree of variance with DOACs, when compared with clinical factors such as renal impairment.

Bleeding and Reversal:

One of the biggest challenges with any anticoagulant is bleeding. Any clinical benefit of preventing thrombosis must be measured against the risk of bleeding. This can be challenging in a low resource setting where laboratory and clinical services are inadequate. DOACs have been shown to have generally lower rates of major bleeding events compared to warfarin in Phase III clinical trials in patients with AF. Apixaban 5 mg twice daily (odds ratio 0.71, 95% confidence interval [95% CI] 0.61 to 0.81), dabigatran 110 mg twice daily (0.80, 95% CI 0.69 to 0.93), edoxaban 30 mg once daily (0.46, 95% CI 0.40 to 0.54), and edoxaban 60 mg once daily (0.78, 95% CI 0.69 to 0.90) all reduced the risk of major bleeding compared with warfarin when maintained at an INR of 2.0-3.0[10]. In patients treated with DOACs, the rate of intracranial hemorrhage was significantly less with the 110mg and 150 mg dabigatran dose (0.23% and 0.30% vs. 0.74% P <0.05), rivaroxaban (0.5% vs. 0.7%, P =0.02), apixaban (0.33% vs. 0.80%, P<0.001), high-dose and low-dose edoxaban (0.39% and 0.26 vs. 0.85%,P<0.001) compared to those treated with warfarin[48-51]. However, rates of major gastrointestinal bleeding were higher in patients treated with dabigatran 110 mg and 150 mg (1.12% and 1.51 % vs. 1.02%,P <0.05) or rivaroxaban (3.2% vs. 2.2%,P<0.001) compared to those receiving warfarin in the 'Randomized evaluation of long-term anticoagulant therapy warfarin, compared with dabigatran' (RE-LY) trial and 'The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation' (ROCKET-AF) trials respectively[48, 49]. Management of bleeding requires halting treatment and modification of dose and administration of a reversal agent to stop bleeding especially when severe or life threatening. In the case of warfarin, Vitamin K is effective at reversing its effects[47], is affordable and readily available in low resource settings. Specific reversal agents for DOACs have not existed until recently and are not yet available on the market in SSA countries. In addition, they are far too costly to use routinely even in high income countries[52, 53]. Concerns about the lack of reversal agents for DOACs may limit their use by prescribers[54] especially in SSA where plasma derived medicinal products that are useful in clinical management of bleeding are expensive and scarce[55] .

Drug monitoring:

Warfarin requires regular monitoring of the International Normalized Ratio (INR) to inform dose adjustment. Warfarin dose can be adjusted using standardized dosing schedules to achieve the desired INR target range[56], and the success of these adjustments is often expressed by the time in therapeutic range (TTR). Higher TTR is generally associated with lower bleeding events and mortality[57]. Numerous studies in SSA show that the median TTR is still low ranging between 29 to 47%[58-61]. This highlights several existing challenges with warfarin therapy in this setting including inadequate patient knowledge[62, 63], and lack of validated dosing algorithms[61]. In clinical trials comparing DOACs to warfarin, study participants on warfarin achieved higher median TTRs between 58 -69% [48-51] which likely reflects patient selection, intensified follow-up and dose adjustment protocols among trial participants which is not reflective of the real-life scenario. High TTRs have also been recorded in patient registries in high income countries[64] where specialist clinics, more frequent monitoring including patient self-testing, guidelines and the use of clinical dosing algorithms may account for better control.

DOACs do not typically require monitoring. However, due to interpatient variability in drug response, it may be necessary to perform monitoring in certain clinical situations. Checking DOAC concentrations may assist in clinical decision-making for patients with extremes of body weight, acute renal injury, recurrent thrombosis and drug-drug interactions[65]. Other patient groups that are not routinely included in clinical trials of DOACs, such as those on antiretroviral therapy (ART) 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[20, 66]. The significance and effect of drug-drug interactions on the efficacy and safety of DOACs in patients on ART is not well studied. Having a measure of pharmacodynamic response (INR in the case of warfarin) is helpful in clinical decision making for patients on long-term concomitant medications, particularly when high doses of anticoagulant are required to overcome the DDI[67]. The lack of a monitoring test in the case of DOACs may be problematic in patients that experience major bleeding events or those that require emergency surgery if there is no quick objective test to monitor drug effects or response to an administered reversal agent.

DOACs may prolong standard clotting tests-prothrombin time (PT), INR and activated partial thromboplastin time (aPTT). However, changes observed in these clotting tests at therapeutic doses are highly variable[68]. A systematic review of 109 studies reporting relationships between DOAC levels and coagulation assay results[68] found that there was variation in performance of standard coagulation tests across DOACs and reagents. Most assays showed insufficient correlation to provide a reliable assessment of DOAC effects. Dilute Thrombin time (TT) or ecarin-based assays were found to show the best correlation with plasma concentrations of dabigatran while anti-factor Xa assays with drug-specific calibrators had the best correlation for the factor Xa inhibitor concentrations[68]. Specific drug Anti-factor Xa assays using reagents and reference ranges that are specific to the SSA population need to be established for DOAC monitoring[69].

Lastly, it is important to consider that INR monitoring is a helpful tool for assessing warfarin adherence. DOAC adherence currently relies solely on adherence assessment tools that include self-reported adherence and other tools that consider drug refills collected which may be inaccurate and overestimate adherence. Adherence is important to achieve target INR and even more important for DOACs given their relatively shorter half-lives. Studies from high income countries comparing medication adherence of warfarin and DOACs show varying results. Some report better adherence to DOACs compared to warfarin, others report similar adherence irrespective of dosing frequency and INR monitoring, while some have reported poorer adherence[70, 71]. Factors influencing anticoagulant adherence in SSA need to be explored especially for DOACs where drug monitoring may not be feasible.

Anticoagulation in Atrial Fibrillation and Valvular Heart Disease

The prevalence of AF is not extensively studied in SSA. The few studies which have been undertaken have reported varying prevalence of AF ranging from 0.3% to 0.7 % in rural communities[72] and more than 4% in urban communities[73, 74]. The prevalence of AF is much higher in patients with known cardiac disease[71] with such patients in SSA more likely to have AF which is due to valvular heart disease (VHD) than those in Europe or North America[75]. This is in part due to the fact that Africa still has a

disproportionately higher prevalence of RHD compared to western countries. 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[75]. Hospital based studies have reported co-existing VHD in 10 to 53% of patients with AF in SSA[76-79]. Unfortunately, the mortality rate of patients with AF, particularly patients with valvular AF, is high ranging from 10% to 40%[77-79] after one year. This has been attributed to late presentation of patients with advanced disease and suboptimal use of oral anticoagulant therapy[76] compounded by suboptimal anticoagulation control in patients who are taking warfarin[77, 79].

The four major Phase III trials comparing warfarin to DOACs -RE-LY, ROCKET AF, Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) and the Effective anticoagulation with factor Xa next Generation in Atrial Fibrillation (ENGAGE-AF) trial) [48-51] were designed to only include patients with non-valvular AF (Table 2). However, a proportion of the enrolled participants in all four trials also had other forms of VHD such as aortic stenosis, aortic regurgitation, mitral regurgitation[80]. The ENGAGE-AF trial also included some patients with prior valve surgery (bioprosthesis replacement, valvoplasty, valve repair)[81]. Sub-group analyses of these trial participants found that DOACs can be safely used in patients with the aforementioned types of VHD[80, 81]. 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, multicenter, randomized open-label trial which has enrolled more than 25% of its participants (1150) from 14 SSA countries[82].

Although still scarce in many countries in this region, heart valve replacement surgery accounts for some of the patients on long term anticoagulation in SSA[59, 60]. Patients with mechanical heart valves were excluded from all four major clinical trials comparing a DOAC to warfarin in patients with AF. Attempts to demonstrate safety of DOACs for this high-risk population have thus far been unsuccessful. The prematurely terminated 'Randomised, phase II study to 'Evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement' (RE-ALIGN) showed that use of dabigatran in patients with mechanical heart valves was associated with increased rates of both thromboembolic and bleeding events[83]. Thrombo-embolic events occurred even when higher dabigatran trough plasma levels were achieved. Jaffer and colleagues demonstrated that mechanical heart valve components induce thrombin generation via the intrinsic pathway and that warfarin is better than dabigatran at inhibiting this process[84]. This *in vitro* study showed that higher doses of dabigatran were needed to achieve the inhibitory effect similar to warfarin (at a target INR range of 2 -3.5) and exceeded those used in the RE-ALIGN study. At the present time, therefore, warfarin will likely remain the anticoagulant of choice in patients with mechanical heart valves.

{Table 2 here}

Anticoagulation in Chronic Kidney Disease

The pathophysiological changes that occur as a result of impaired kidney function increase the risk of both thromboembolism and bleeding in patients with chronic kidney disease (CKD)[85]. As a result of this unique paradox, effective anticoagulation in these patients is difficult and requires more frequent INR monitoring and dose adjustment of warfarin[86] and DOACS[87]. Apixaban 5mg administered twice daily, dabigatran 110mg or 150mg twice daily, rivaroxaban 15 mg once daily and edoxaban 30mg once daily have been found to be as safe and efficacious as adjusted-dose warfarin in AF patients with moderate CKD (CrCl 30 -59ml/min)[88, 89] .However, in patients with severe renal impairment (CrCl 15-29ml/min) and end stage renal disease (ESRD) (CrCl <15ml/min), the efficacy and safety of warfarin and DOACs remains questionable as these patients were excluded from the landmark trials comparing DOACs to warfarin in AF. Data from two systematic reviews and meta-analyses of observational studies in patients with ESRD on dialysis suggest that warfarin use has no stroke-preventing benefit and is associated with an overall increased risk of bleeding[90, 91]. Similarly, a limited number of observational studies suggest that DOACs show no significant difference with warfarin in reducing stroke outcomes in haemodialysis patients[88] with patients on dabigatran and rivaroxaban having higher risk of major bleeding compared to those on warfarin[88].The current guidance on DOAC dose adjustment in patients with severe renal impairment is derived from pharmacokinetic modelling studies and manufacturer recommendations[92, 93] (Table 1). In patients with ESRD, DOACs are not recommended due to absence of conclusive evidence from prospective randomised controlled trials[94]. An individualised approach is therefore needed to assess risk and benefit of anticoagulation for each patient with CKD[85, 94]particularly those with severe renal impairment and ESRD due to the scarcity of evidence on dose adjustment in these patients .Patients' renal function monitoring using estimated creatinine clearance using Cockcroft-Gault method needs to be integrated into routine anticoagulation care of SSA patients on warfarin and even more so for those using DOACs given the lack of drug monitoring for DOACs.

Anticoagulation in pregnancy

Anticoagulation in pregnancy is a challenging problem and especially so in low income settings. All available oral anticoagulants may cause maternal and fetal complications. Most guidelines recommend use of heparin during pregnancy as heparin does not cross the placenta therefore eliminating possibility of direct drug related embryopathy. However, heparins are expensive to purchase and store, are administered intravenously or subcutaneously and therefore adherence is a potential hindrance to long term use. In addition, low molecular weight heparin which is the preferred option in pregnancy may require monitoring of anti Xa levels due to a myriad of physiological changes that alter its pharmacokinetics and may increase risk of thrombotic or bleeding complications in mothers[84]. It is not uncommon for women in SSA on long term oral anticoagulation such as those with mechanical heart valves to continue using warfarin even during pregnancy[95, 96]. Warfarin is an effective anticoagulant even in pregnancy: a meta-analysis of 46 prospective and retrospective studies on anticoagulation for pregnant women with mechanical heart valves found that using VKAs with standard (2.5-3.5) INR target throughout pregnancy was associated with the lowest pooled proportions of maternal mortality and thromboembolic complications followed by sequential treatment (LMWH in first trimester followed by

warfarin) and LMWH[97] . However, there remains a risk of fetal complications if used in first trimester particularly in the second half of this period when organ formation is taking place[95]. It is widely accepted that the warfarin-related fetal complications are dose related. Use of low doses of warfarin (<5mg) to attain a target INR 1.5-2.5 in pregnancy has been shown to have better pregnancy outcomes with reduced fetal embryopathy and mortality[98] . This may be useful especially in pregnant patients on long term prophylaxis due to recurrent DVT and those with mechanical heart valves who may not be able to afford heparin.

Currently, DOACs are not licensed for use in pregnancy. Just like warfarin, DOACs cross the placenta and can therefore cause both maternal and fetal hemorrhage. Animal studies in both rats and rabbits have demonstrated toxic effects of dabigatran and edoxaban during pregnancy such as post implantation loss, abnormal ossifications and liver abnormalities[99, 100]. In addition, DOACs have been reported to be excreted in breast milk. Case reports of mothers taking rivaroxaban at standard doses indicate that it is excreted in breast milk albeit at low relative infant doses[101, 102]. In contrast, small lactation studies have demonstrated warfarin to be undetectable in the breast milk and infant plasma when mothers have received a range of doses[103-105]. It is yet to be established if presence of DOACs in breastmilk has implications for the nursing infant and hence caution must be exercised when using DOACs in breastfeeding mothers. There is no conclusive evidence available at the time of writing to support use of any of the DOACs in pregnant or breastfeeding women.

Cost of Warfarin Versus DOACs

In order to evaluate overall treatment cost of anticoagulation, consideration must be given to direct costs such as the cost of medication, expenses associated with the monitoring of anti-coagulant treatment, admissions due to complications and additional treatments to achieve effective international normalized ratio (INR) values[106]. In addition, indirect costs such as lost employment time and productivity associated with anticoagulation[107] should be estimated.

The biggest hindrance to using DOACs especially in low income settings has been inaccessibility and high cost of drug compared to VKAs. In Uganda, a single 5mg warfarin tablet costs approximately 0.2 USD, which is significantly lower than the 2 to 4 USD that would be required to purchase a single 15mg tablet of rivaroxaban[61]. A retrospective study of patients with DVT in Turkey found that treatment with warfarin was more economical than rivaroxaban when all associated costs were evaluated, despite rivaroxaban yielding lower annual costs for outpatient visits and annual costs associated with complications due to the higher acquisition costs for rivaroxaban (362.6 USD for rivaroxaban versus 71.55 +/- 31.01 USD for warfarin)[106]. In another retrospective cohort study in Italy, mean direct cost per patient per year was higher for patients treated with DOACs than for patients treated with VKA, the cost difference in part driven by drug costs (900 USD for DOAC versus 20 USD for VKA patients)[108]. Unlike warfarin, there are no generic options for DOACs in SSA. Xarelto®, is currently the only brand of rivaroxaban registered in Uganda[109] and Zimbabwe[110] while Pradaxa® is the only brand of dabigatran available in countries where it is registered such as Kenya[111] and Nigeria[112].

Patients on warfarin generally require more outpatient visits due to INR monitoring and accompanying dose adjustments than those on DOACs[106]. Diken and colleagues found that average annual number of outpatient clinic visits were significantly higher in patients on warfarin compared to those taking rivaroxaban[106]. This subsequently drove up the annual average outpatient costs for the former. Similarly, Annachiara and colleagues found that costs for specialist visits and lab tests were at least twice as high for patients taking VKAs compared to those taking DOACs[108]. However, the frequency of INR testing also depends on the stability of patients' INR results with unstable patients typically requiring more frequent monitoring following dose adjustment. The cost of INR testing may vary depending on the country and location within a given country. In a private care setting in South Africa, the cost of INR monitoring was estimated to be 6 USD[113]. This is similar to pricing in Uganda, where the cost of an INR test is 5 USD in urban hospitals[61] 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 SSA countries like South Africa whereas they are paid for out of pocket in countries like Uganda[61] where government health insurance schemes do not yet exist.

Costs incurred due to hospital admission caused by complications such as bleeding appear to be higher in patients taking warfarin than those on DOACs[106, 114] due to higher overall rates of bleeding events with warfarin. This has been shown in all major clinical trials comparing safety and efficacy of warfarin to each of the DOACs. However, these clinical trials have been predominantly conducted in high income countries. This excluded African patients who may show varied responses to DOACs than those reported in the predominantly Caucasian and Asian trial populations. For this reason, despite scarcity of efficacy and safety data on DOACs in sub-Saharan Africans, cost effectiveness studies based on trial results should be interpreted cautiously given the potential effects of differences in patient populations. Real world observational studies in SSA countries may provide more reliable data for real time estimation of costs associated with complications of anticoagulants.

Travel costs may be difficult to compare across the different sub-Saharan countries given the differences in the mode, cost and duration of travel to access health facilities. Similarly, estimating cost of lost employment time may be difficult due to differences in wages across the region. However, warfarin treatment is associated with more clinic visits due to INR monitoring and hence is expected to have higher indirect costs. Indirect costs in addition to costs of drugs need to be considered in patients who are eligible for treatment with DOACs or warfarin.

Conclusion

Despite the pitfalls of warfarin anticoagulation stemming from its complex pharmacokinetics and interaction profile, it remains an important option in particular patient populations requiring anticoagulation in SSA; and who can access INR monitoring. Widespread use of DOACs which have preferable pharmacokinetic profiles has been limited partly due to their significantly higher cost and safety concerns in special patient populations where they are yet to be studied.

Conflict of interest statement

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Tables

Table 1 Pharmacokinetic characteristics and notes on clinical use of DOACs and warfarin

Drug	**Pharmacokinetics**	**Points to note on clinical application**
Apixaban	Absolute bioavailability is approximately 50%[20] T_{max} is 1.5-3.3 hours[30] Eliminated primarily in feces and urine[31]. Half- life is approximately 12 hours[30].	Dosing in patients with kidney impairment[32]: • Mild or moderate renal impairment: -DVT/PE treatment or prevention: No dose adjustment required -NVAF: Patients with serum creatinine ≥1.5 mg/dl with weight ≤ 60kg and or age ≥ 80 years- a lower dose of 2.5mg twice daily is recommended. • Severe renal impairment (creatinine clearance 15-29ml/min): -DVT/PE treatment or prevention: Use with caution -NVAF: a lower dose of 2.5mg twice daily is recommended • ESRD and patients on hemodialysis: Apixaban is not recommended DDIs: Rifampicin co-administration reduces apixaban exposure[20] Specific reversal agent: Andexanet alfa[33].
Dabigatran	Absolute bioavailability is approximately 6.5%[34] T_{max} is 1.25- 1.5hours[34] Eliminated primarily in feces and urine[34] Half-life is 8-10 hours[34]	Dosing in patients with kidney impairment[35]: • Mild renal impairment (CrCl 50- ≤80mL/min): No dose adjustment required • Moderate renal impairment (CrCl 30-50 ml/min): Dose reduction from 150mg to 110 mg twice daily should be considered in patients with high risk of bleeding • Severe renal impairment (CrCl <30ml/min): Dabigatran treatment is contraindicated DDIs: Rifampicin significantly reduces dabigatran bioavailability. Co-administration is not recommended[19]. Specific reversal agent :Idarucizumab[36]
Edoxaban	Absolute bioavailability is approximately 62%[37]. T_{max} is 1-2 hours[38]. Eliminated primarily in feces and urine. Renal clearance accounts for about 35% of administered dose[39]. Half-life is 5-11 hours[38]	Dosing in patients with kidney impairment[40]: • Mild renal impairment: Recommended dose is 60 mg once daily • Moderate to severe renal impairment (CrCl 15-50mL/min)-Dose reduction to 30 mg once daily is recommended • ESRD: (CrCl < 15ml/min) or on dialysis- use of edoxaban is not recommended DDIs: Use with caution with Rifampicin and other p-gp inducers[40] Specific reversal agent: None
Rivaroxaban	Absolute bioavailability is 80-100% for 2.5mg and 10 mg dose[41].	Dosing in patients with kidney impairment[44]: • Mild renal impairment: No dose adjustment needed

	T_{max} is 3-4 hours[42]. Eliminated primarily in urine with 66% of dose excreted renally(36% unchanged drug) and 28% in feces[43]. Terminal elimination half-life is 5-9 hours[41]	• Moderate or severe renal Impairment: Use with caution. Recommended dose is 15mg once daily. • ESRD: Use is not recommended DDIs: Rivaroxaban is not recommended in patients receiving concomitant treatment with systemic azole-antimycotics like ketoconazole or HIV protease inhibitors[44] Specific reversal agent: Andexanet alfa[33]
Warfarin	Bioavailability is close to 100%[45]. T_{max} is 2 to 6 hours[12]. Eliminated almost entirely by hepatic metabolism with metabolites primarily renally excreted[12]. Half- life is 20 to 60 hours[12]	Dosing in patients with kidney impairment: Patients with renal disease are at increased risk of over coagulation and require more frequent INR monitoring DDIs: Several drugs interact directly or indirectly with warfarin. Consult product information of any new concomitant medication for guidance on dose adjustment and INR monitoring[46] Reversal agent: Vitamin K[47]

CrCl: creatinine clearance; DDI: drug-drug interaction; DVT: deep venous thrombosis; ESRD: end-stage renal disease; INR: international normalized ratio; NVAF: non-valvular atrial fibrillation; PE: pulmonary embolism; p-gp: p-glycoprotein; T_{max}: time taken to reach maximum plasma concentration

Table 2 Phase III Randomized Clinical Trials comparing Warfarin to DOACs 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	18113 participants White:70% Asian:15.9% Black:1 % Other:13.1%	-History of heart valve disorder (prosthetic valve or hemodynamically relevant valve disease) -Severe renal impairment (estimated CrCl ≤ 30ml/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	14264 participants Ethnicity not described	-Hemodynamically significant mitral valve stenosis -Prosthetic heart valve patients -Pregnancy or breastfeeding -Known HIV infection at screening Calculated CrCl <30ml/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 one additional risk factor for stroke	South Africa	18201 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 <25ml/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 two dose regimens of once-daily edoxaban with warfarin in patients with atrial fibrillation who were at moderate-to-high risk for stroke.	South Africa	21105 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 <30ml/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 stoke prevention in RHD and AF	Botswana, Cameroon, Ethiopia, Kenya, Malawi, Mozambique, Nigeria, Rwanda, South Africa, Sudan,	4565 participants SouthAsian:17.3% Chinese:5.1%Other Asian:17.6% Arab:17.1% Black African:25.3% Latin	-Presence of a mechanical valve -Severe renal insufficiency (eGFR < 15 ml/min) -Pregnant women and women of child bearing potential not using effective contraception

		Tanzania, Uganda, Zambia, Zimbabwe	American:7.6% Other:10.1%	

AF: atrial fibrillation; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; HIV: human immunodeficiency virus; RHD: rheumatic heart disease; SSA: sub-Saharan Africa