Review Article

Anticoagulation in Sub-Saharan Africa with the Advent of Non-Vitamin K Antagonist Oral Anticoagulants

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Abstract

Background: Since the approval of warfarin, a Vitamin K antagonist anticoagulant (VKA), no other oral anticoagulant existed for patients who needed long-term anticoagulation therapy until the recent introduction of non-VKA oral anticoagulants (NOACs). NOACs came to fill in therapeutic gaps associated with VKA. Dedicated anticoagulation clinics has improved the outcome of using VKA. However, with the arrival of NOACs, it is not clear how they will fit into these clinics. **Methods:** We searched PubMed, Google Scholar, Medline, and African Journals OnLine for articles on anticoagulation management and NOACs. **Results:** There were very few dedicated anticoagulation management centers in Sub-Saharan Africa, notably in Nigeria, South Africa, Kenya, Uganda, Namibia, Ghana, Botswana, Namibia, and Cameroun and warfarin was the anticoagulant used. NOACs were not used regularly. None of these anticoagulation clinics had incorporated NOACs management into their routine service as was done for VKA. **Conclusion:** Anticoagulation clinics in Sub-Saharan Africa must include NOACs as part of their area of service in addition to warfarin. The use of NOACs in Africa will leap frog if proper anticoagulation management policy and structure are laid out, the cost of NOACs are reduced, and emphasis is given to retraining of staff.

Keywords: Anticoagulation management, NOACs, Sub-Saharan Africa, warfarin

Introduction

Warfarin was approved as an anticoagulant in 1954 and has maintained the lead as the most commonly prescribed anticoagulant for many decades.[1] Countless number of patients have benefited from the life-saving benefits of warfarin. Perhaps, warfarin's most famous patient was President Dwight Eisenhower who had myocardial infarction in 1955.[1]

Since the approval of warfarin, no other oral anticoagulant existed for patients who needed long-term anticoagulation therapy until the recent introduction of non-V itamin K antagonist oral anticoagulants (NOACs). The term non-VKA oral anticoagulants is now generally accepted following previous labeling as novel oral anticoagulants (NOACs), direct acting anticoagulants (DOACs), target-specific oral anticoagulant, oral direct inhibitor, and specific oral direct anticoagulant.[2]

One of the problems with the era of widespread clinical application of warfarin was the laboratory method used for dosage control, the prothrombin time (PT). This arose because the result (s) for a PT performed on a normal individual will vary according to the type of analytical system employed. This is due to the variations between different types and batches of manufacturer's tissue factor used in the reagent to perform the test.[3]

This was solved with the reporting of results in International normalized ratio (INR). This provided a scientific method of monitoring the effect of warfarin and steered the patient away from under- and overcoagulation.[3] However, there were so many variables that effected the pharmacodynamics and pharmacokinetics of warfarin. This ranged from drug–drug interaction, food–drug interaction, and even disease–drug interaction.[4] This made monitoring of anticoagulant effect of warfarin cumbersome.

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Warfarin interacts with more than 250 drugs.[5,6] This meant that prescription and use of many drugs for patients on warfarin needed caution and vigilance to be able to keep the patient within therapeutic range and still stir the patient away from excessive bleeding and thrombosis.

Patients on warfarin anticoagulation also needed to watch food intake. Vitamin K-rich foods, Vitamin K-containing supplements, and green leafy vegetables will reduce the INR.[5] Many drugs with an antiplatelet effect like aspirin and other nonaspirin nonsteroidal anti-inflammatory drugs will increase bleeding tendency.[7]

Liver disease can lead to increased bleeding through liver's inability to synthesize clotting factors, the presence of concomitant thrombocytopenia due to portal hypertension, and through the presence of esophageal varices.[7] Hypothyroidism decreases the catabolism of the Vitamin K clotting factors and therefore decreases INR.[8] Hyperthyroidism will do the reverse.[4] Congestive heart failure can cause hepatic congestion of blood flow and inhibit warfarin metabolism, increasing INR particularly with frequent exacerbations or advanced heart failure.[7]

Patients with severe renal impairment or chronic kidney disease (CKD) will require a significantly reduced dose of warfarin to achieve therapeutic INR in comparison with those with normal kidney function. Patients with a CrCl of 30–59 mL/min/1.73 m^2 will need a 10% lower maintenance dose, while those with levels of <30 mL/min/1.73 m^2 a 20% lower dose. This may be related to the downregulation of cytochrome P450 in CKD.[9]

Care of patients on long-term anticoagulation needed drugs that had markedly reduced drug interaction, less food and disease interaction, and could provide the convenience and noninvasiveness of oral drugs. NOACs came to fill in some of the gaps presented by warfarin. The advantages and disadvantages of NOAC when compared with warfarin are outlined in Boxes 1 and 2.

In 2010, the U. S. Food and Drug Administration (FDA) gave approval for the first NOAC, an oral direct thrombin inhibitor dabigatran (Pradaxa).[10] This was followed in 2011 with approval of the oral direct factor Xa inhibitor rivaroxaban (Xarelto) and again in 2012 with the FDA approval of the oral factor Xa inhibitor apixaban (Eliquis).[10]

NOACs are relatively new in Africa and how it will fit into the management architecture of anticoagulation services in Sub-Saharan Africa (SSA) that is weak, and in some cases, nonexistent is not known. We sort to examine the anticoagulation management services in Sub-Saharan Africa and see how it will cope with the introduction and use of NOACs.

Box 1: Advantages of NOACs over warfarin

- Quick onset of action obviates need for heparin/low-molecular-weight heparin bridging
- Quick offset of action simplifies periprocedural management and reduces need for reversal agents
- Decreased risk of intracranial bleeding translates to safer anticoagulant therapy
- There are fewer drug and food interactions and so predictable anticoagulant effect

Box 2: Disadvantages of NOACs over warfarin

- Reversal agents for oral factor Xa inhibitors not yet licensed and so physicians are concerned about uncontrollable bleeding. Management of patients who require urgent intervention may be complicated
- There is limited access to standardized assays for drug level measurement and this complicates identification of bleeding patients who require reversal and timing of urgent surgery or intervention
- The use of NOACs in patients with severe renal failure is contraindicated
- Fecal excretion of active anticoagulant may predispose at-risk patients to gastrointestinal bleeding
- Higher cost of NOACs will limits use in some countries and patient groups

Methods

We searched PubMed, Google Scholar, Medline, and African Journals OnLine for articles on anticoagulation management and non-VKA s oral anticoagulants. The search was from January 1990 to January 2020, a 30-year period. Search words included "anticoagulation clinics," "anticoagulation management services," "Dedicated anticoagulant clinics," "Non vitamin K antagonist oral anticoagulants" (NOACs), and "Vitamin k antagonist oral anticoagulants," all with the word "Africa." We also searched the website of main Teaching and Specialist Hospitals seeking to find out those centers with active anticoagulation services. We defined anticoagulation clinics as services provided by specialists including cardiologists, hematologists, trained nurses, and clinical pharmacists dedicated toward achieving effective and safe anticoagulation. Centers where anticoagulants were prescribed without any definite program to organize the services for improved patient safety and effective care were excluded.

Results

Anticoagulation is prescribed in many hospitals in SSA, but dedicated anticoagulant clinics or anticoagulation management services were found in very few countries.

Nigeria topped the list with up to six tertiary centers having anticoagulation clinics with consultant cardiologists and or hematologists in charge. South Africa had four anticoagulation clinics. Uganda had 3 centers providing anticoagulation services. Anticoagulation management services were also in place in one center each in Ghana, Kenya, Cameroun, Namibia, Ivory Coast, Ethiopia, and Botswana (see Table 1). Most other countries prescribed anticoagulation in the setting of routine medical care.

The anticoagulation clinics were mainly involved in the management and monitoring of warfarin in the different clinical conditions it is indicated. NOACs were not inculcated in the

dedicated anticoagulation management services. NOACs were prescribed by specialist who were mainly cardiologists and hematologists who had adequate knowledge of their use. In some centers, the consultant worked with pharmacists and nurses to provide daily anticoagulation management services; otherwise, only once or thrice weekly service was delivered. Pharmacist-run anticoagulation clinic was found in Kenya. Nurse-run anticoagulation clinic was also found in South Africa. Most of the anticoagulation management services were provided in tertiary hospital setting. It is only in South Africa that anticoagulation services were provided in primary and secondary health center setting.

Discussion

The use of NOACs is guided by their pharmacokinetic and pharmacodynamic characteristics. The relationship between dose, drug concentration, and effect defines the therapeutics of any medicine. This knowledge is useful in the therapeutics of NOACs.

Therapeutics of anticoagulants

The NOACs have a rapid onset of action with peak concentrations achieved in 1–4 h. The half-life varies from 5 to 9 h for rivaroxaban, 12 h for apixaban, 9–14 h for edoxaban and 12–17 h for dabigatran.[11-14] Rivaroxaban and apixaban are metabolized via the cytochrome P450 system, particularly cytochrome P450 isoenzyme 3A4 (CYP3A4), whereas edoxaban and dabigatran undergo little cytochrome P450-mediated metabolism. All of the NOACs are substrates for P-glycoprotein (P-gp). The NOACs are excreted through the kidneys with dabigatran having up to 80% and apixaban the lowest, 25% excretion.

NOACs are indicated for the prevention of recurrent deep venous thrombosis (DVT) and pulmonary embolism (PE) in adults, treatment of DVT and PE and stroke prevention for patients with atrial fibrillation (AF). ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, and ROCKET AF trials demonstrated that NOACs had at least noninferior reductions in stroke and systemic embolism compared with warfarin.[15] Apixaban, dabigatran, edoxaban, and rivaroxaban are indicated by the European Medicines Agency and FDA for patients with nonvalvular AF defined as AF in the absence of rheumatic MS, a mechanical or bioprosthetic heart valve, or mitral valve repair.[16] In addition, the NOACs were associated with similar or lower rates of major or clinically relevant nonmajor bleeding and significantly decreased rates of intracranial bleeding compared with warfarin.[17-20]

NOACs are contraindicated in patients who have mechanical or bioprosthetic heart valve; the findings of the RE-ALIGN study showed that dabigatran was less effective than warfarin for stroke prevention in patients with mechanical heart valves.[21] The explanation may be because medical devices, such as heart valves, trigger clotting by activating factor XII and may locally generate factor Xa and thrombin in concentrations that exceed those of the NOACs.

In contrast, by lowering the functional levels of the Vitamin K-dependent clotting factors, warfarin attenuates thrombin generation regardless of the trigger.There are also studies that show that warfarin attenuates thrombin generation induced by mechanical valves at INR values of ≥1.5, whereas dabigatran concentrations in excess of 260 ng/mL are required for equivalent suppression of thrombin generation.[21] These dabigatran concentrations are 5-fold higher than the targeted trough level of 50 ng/mL used in the RE-ALIGN study.[21] It is not known whether if by attenuating thrombin generation, rivaroxaban, apixaban, or edoxaban would be better than dabigatran for prevention of clotting on mechanical valves.

The main adverse effects of NOACs include bleeding, but there are also non hemorrhagic side effects such as hypersensitivity reactions, leukocytoclastic vasculitis, and hair loss. A study that investigated the associations between direct oral anticoagulants (DOACs) and risks of bleeding, ischemic stroke, venous thromboembolism, and all-cause mortality compared with warfarin showed Figure 1 is the Prisma diagram depicting the selection process that apixaban was found to be the safest drug, with reduced risks of major, intracranial, and gastrointestinal bleeding compared with warfarin. Rivaroxaban and low-dose apixaban were, however, associated with increased risks of all-cause mortality compared with warfarin.[22]

NOACs are associated with fewer drug–drug interactions and drug–disease interactions than VKAs, but there is need to keep an eye on the pharmacokinetics of medications coadministered and all comorbidities when NOACs are prescribed. As mentioned previously, rivaroxaban and apixaban are metabolized via the cytochrome P450 system, particularly CYP3A4, whereas edoxaban and dabigatran undergo little cytochrome P450-mediated metabolism. Therefore, the concentrations of rivaroxaban and apixaban can be increased or decreased by potent inhibitors or inducers of CYP3A4, respectively.[23,24] All of the NOACs are substrates for P-gp and potent inhibitors or inducers of P-gp can increase or decrease

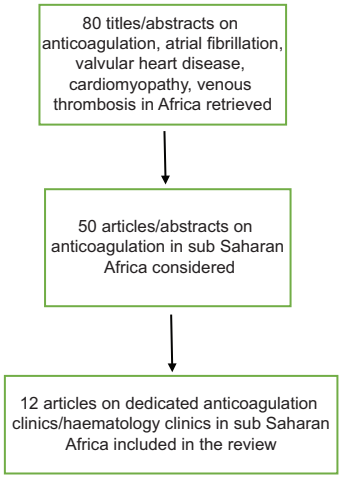

Figure 1: The selection process

Table 1: Chart of published articles describing dedicated anticoagulation clinics in sub-Saharan Africa

Countries	Published article
Nigeria	1. Anakwue RC, Nwagha T, Ukpabi O, *et al*. A survey of clinicians practice patterns in anticoagulation therapy & prophylaxis in South East Nigeria. Haematol Int J 2018;2:3 2. Anakwue R, Nwagha T, Ukpabi OJ, *et al*. Clinicians-related determinants of anticoagulation therapy and prophylaxis in Nigeria. Ann Afr Med 2017;16:164-9 3. Available from: file:///C:/Users/Dr%20Ralph%20A/Documents/Anticoagulation%20%20Nigeria%201c%20%20Specialist%20hospitals.pdf
South Africa	1. Ebrahim AI, 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. South Afr Med J 2018;108:490-4. 2. Semakula JR, Mouton JP, Jorgensen A, *et al*. A cross-sectional evaluation of ve warfarin anticoagulation services in Uganda and South Africa
Cameroun	Etoundi PO, Esiéne A, Bengono RB, *et al*. La maladie thromboembolique veineuse. Aspects épidémiologiques et facteurs de risque dans un hôpital Camerounais 2015; Health sciences and disease: 16:4
Ghana	Olayemi E. Time in Therapeutic Range (TTR) of Ghanaian VTE Patients on Warfarin. ISTH Acad 2019;264830
Kenya	Nyamu DG, Guantai AN, Osanjo GO, *et al*. Trends of anticoagulation control among adult outpatients on long-term Warfarin therapy in a Tertiary Teaching and Referral Hospital in Kenya. East Afr Med J 2018;95:7
Namibia	Jonkman LJ, Marvelous P, *et al*. Assessment of anticoagulation management in outpatients attending a warfarin clinic in Windhoek, Namibia. Drugs Ther Perspect 2019;35:341-6
Ivory coast	Coulibaly I, Anzouan-Kacou JB, Konin KC, *et al*. Atrial fibrillation: epidemiological data from the Cardiology Institute in Abidjan, Cote d'Ivoire. Med Trop 2010;70:371-4
Ethiopia	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;6:389
Botswana	Mwita JC, Francis JM, Oyekunle AA, *et al*. Quality of anticoagulation with warfarin at a tertiary hospital in Botswana. Clin Appl Thromb Hemost 2018;24:596-601

the plasma concentrations of the NOACs, respectively. Table 2 outlines important drug–drug interaction.

There are no foods to avoid when taking NOACs because these drugs do not interact with any food. This is unlike warfarin where green leafy vegetables affect its action.[25] Large amounts of alcohol may cause or trigger AF and can also increase the risk of bleeding. Therefore, it is recommended take not more than one drink daily.[25]

Since dabigatran and to a lesser extent, rivaroxaban and apixaban are excreted by the kidneys, drug accumulation can translate into accentuated anticoagulant effects.[26,27] Severe renal impairment and end-stage renal disease preclude use of these new oral anticoagulants and therapy with warfarin is recommended in patients with such conditions. NOACs are contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Turcotte-Pugh C cirrhosis.[28,29] Rivaroxaban should also not be used in AF patients with Child B liver cirrhosis.

The use of NOAC in African countries will lack behind that of developed countries for some time. The first reason is the high cost of NOACs compared with warfarin. When cost is the only considered factor, warfarin rates much higher than NOAC as the preferred anticoagulant in most settings in Africa. However, other factors weigh even higher when the use of anticoagulants are considered. Benefits and risk factors are also important. Benefits of the anticoagulant therapy includes reductions in stroke and all-cause mortality, while risks include intracranial hemorrhage, gastrointestinal hemorrhage, minor bleeding and myocardial infarction.[30]

A structured benefit-risk assessment by IMI-PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by European Consortium) analyzed the benefit–risk and cost assessment of oral anticoagulants used in the management of AF and came to the conclusion that apixaban should be considered as the preferred anticoagulant option, due to a better benefit–risk balance and a minor cost influence, followed by dabigatran, warfarin, and rivaroxaban. The task before the physician is to convince the patient-needing anticoagulation in African setting where payment is out-of-pocket because of the poorly developed health insurance system that warfarin is not the preferred anticoagulant in spite of the very low cost.

The second reason why the use of NOACs may not be the first choice of anticoagulant for some time is the considerable knowledge gap and poor anticoagulation management infrastructure in Africa. We had reported a multicenter study in Nigeria which involved 528 clinicians working in tertiary hospitals.[31] The aim was to evaluate clinicians practice patterns in anticoagulation therapy and prophylaxis in Nigeria. We discovered that only 52 (9.8%) respondents claimed that their institutions had an anticoagulation policy. The most prescribed anticoagulation agent was low-molecular-weight heparin (adjusted odds ratio [AOR]: 163, 95% confidence interval [CI]: 0.85–0.3.14, $P = 0.19$) and warfarin (AOR: 0.5, 95% CI: 0.28–0.88 $P = 0.02$), while the fondaparinux was least prescribed (AOR: 1.74, 95% CI: 0.61–5.0 $P = 0.44$). NOACs where infrequently prescribed. Only 193 (36.6%) of the respondents routinely prescribed anticoagulation therapy when indicated.

Table 2: Non-Vitamin K antagonist oral anticoagulants drug-drug interactions

Class	Drugs	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Strong P-gp inhibitors (also CYP3A4 inhibitors)	Ciclosporin, dronaderone, itraconazole, ketoconazole, posaconazole, tacrolimus, voriconazole	Combination contraindicated	Strong recommendation not to use	Strong recommendation not to use	Reduce dose to 30 mg daily if on ciclosporin, dronaderone, erythromycin or ketoconazole
Other strong P-gp inhibitors (also CYP3A4 inhibitors)	Amiodarone, clarithromycin, quinidine, verapami	Caution. If on verapamil give 110 mg twice daily	Avoid use particularly in renal impairment	Caution	Caution
Protease inhibitors (Pgp inhibitors and CYP3A4 inhibitors)	Ritonavir, telaprevir	Concomitant use not recommended	Strong recommendation not to use	Strong recommendation not to use	No data
Strong P-gp and CYP3A4 inducers	Carbamazepine, phenobarbital, phenytoin, primidone rifampicin, St John's Wort	Combination should be avoided	Combination should be avoided	Combination should be avoided	Use with caution
Other anticoagulants	E.g. LMWH, warfarin, UFH, fondaparinux	Combination contraindicated except when switching therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter	Combination contraindicated except when switching therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter	Combination contraindicated except when switching therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter	Combination contraindicated except when switching therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
Others	Aspirin, clopidogrel NSAID's	Combination not recommended. A careful risk-benefit assessment should be made	Combination not recommended. A careful risk-benefit assessment should be made	Combination not recommended. A careful risk-benefit assessment should be made	Combination not recommended. A careful risk-benefit assessment should be made
	Prasugrel, ticagrelor	Combination not recommended	Combination not recommended	Combination not recommended	Combination not recommended

LMWH: Low-molecular-weight heparin, UFH: Unfractionated heparin, NSAID's: Nonsteroidal anti-inflammatory drugs

The third reason is the fear of bleeding, particularly given the background of the lack of specific antidote to NOACs. However, the outcome of patients with major bleeds is no worse with the NOACs than with warfarin. Many trials including Randomized Evaluation of Long-Term Anticoagulant Therapy with Dabigatran Etexilate (RE-LY) trial, Efficacy and Safety Study of Rivaroxaban with Warfarin for the Prevention of Stroke and Noncentral Nervous System Systemic Embolism in Patients with Nonvalvular AF (ROCKET-AF) trial sand Apixaban for the Prevention of Stroke in Subjects with AF (ARISTOTLE) trial have demonstrated that there is no evidence to support the belief that the lack of specific antidotes renders bleeding events with the NOACs more dangerous than those with warfarin.[10]

Other reasons include the fact that the use of NOAC has not been well validated in African subjects.[32] Indeed a significant limitation of all the NOAC trials with regard to the use of these drugs in the African population is that none of the trials included a large number of patients from Africa, and the percentage of black subjects overall was small.[32] Africans also have a disproportionably higher number of subjects with valvular (rheumatic) AF in whom NOAC is not indicated.

We do not have data needed for dosing of the NOACs in patients at extremes of body weight. The doses of apixaban and edoxaban are reduced in patients with low body weight, those of dabigatran and rivaroxaban are not.[10] Whether dose adjustment is needed for patients with body weight >150 kg is unknown because few such patients were included in the clinical trials.

The NOACs have been marketed as not needing monitoring. However, the RELY trial showed a correlation between dabigatran levels and bleeding and stroke outcomes in patients.[33] Hence, monitoring may be required to optimize the dosing of NOACs. However, tests to measure drug levels are not widely available, the within patient variability in drug levels is sufficiently wide that single measurements may provide misleading information, and the correlation between drug levels and clinical outcomes is confounded by important clinical characteristics, such as age, renal function, and concomitant medications.[33]

Information on the use of NOAC in Africa is not easily available because it is relatively new in Africa even though dabigatran, the first NOAC has been in use since 2010.

Table 3: The different areas of emphasis between Vitamin K antagonist clinic and non-Vitamin K antagonist anticoagulation clinic

Parameters	VKAs clinic	Non-Vitamin K antagonists anticoagulantion clinic
Baseline tests	Hb, liver function test, kidney function test. Repeat as and when necessary	Hb, liver function test, kidney function test. Repeat yearly or more frequent in patients with renal impairment, change in drug or clinical state or age >75 years. NOACs are contraindicated for patients with Child-Pugh category C hepatic insufficiency and CrCl of 15-30 mL/min
Monitoring tests	INR is needed to ensure time within therapeutic range	Activated partial thromboplastin time or dilute thrombin time for dabigatran, aPTT >2.5 times control may indicate overanticoagulation Prothrombin or anti-Factor Xa assays for direct Factor Xa inhibitors are done not as a regular monitoring tests but in emergency conditions
Determination of clinical end point	Absence of thrombotic events and time within therapeutic range	Absence of thrombotic events
Drug-drug interactions	Very important	Important
Drug-food interactions	Very important	Less important
Revisits	Monthly initially and then longer depending on INR, less frequent if within TTR	3-6 months
Most important determinant of safe and effective anticoagulation	INR	Adherence to medication
Half-life of drug and implication	Long half-life and skipping of drug for 1-2 days may not have significant implication	Short half-life, so skipping of drug for 1-2 days will affect benefit of anticoagulation
Education	Targeted on drug-drug interaction, drug-food interaction	Targeted on adherence with shorter half-lives than warfarin, adherence to the NOACs is essential. Care giver education is very important

Hb: Hemoglobin, NOACs: Non-Vitamin K antagonist oral anticoagulants, INR: International normalized ratio, CrCl: Creatinine clearance, aPTT: Activated partial thromboplastin time, TTR: Time in therapeutic range, VKAs: Vitamin K antagonist anticoagulants

Approvals for NOAC in Africa started in 2011 and dabigatran and rivaroxaban are now widely in use in Namibia,[34] Kenya[35] South Africa,[36] Nigeria.[37] Uganda[38] and other countries.[32]

The use of warfarin has declined from 87.5% to 72% through 2008–2014,[39] compared to that of NOAC that has increased to 15.5% globally. In 2016, there are 4,210,000 prescriptions for NOAC in the USA alone. Indeed, NOAC prescriptions exceeded those for warfarin in outpatient office visits for AF, with rivaroxaban being the most frequently prescribed DOAC (47.9%), followed by apixaban (26.5%) and dabigatran (25.5%).[40,41]

Anticoagulation management

In the USA, more than half of the anticoagulation clinics have adjusted their practice to cater for the needs of patients on NOACs as well as those taking warfarin.[40,41] About 10% of the volume of service by these clinics are due to patients on NOACs.[41] This proportion will increase as more patients are placed on NOACs.

Before the advent of NOACs, anticoagulation management service had existed for patients on warfarin and other anticoagulants. Anticoagulation management service is fairly well developed in USA and Europe and nonphysicians including clinical pharmacists and clinical nurses are now part of the staff mix. There are well established anticoagulation clinics run by clinical pharmacists and clinical or registered nurses who prescribe, order laboratory tests and adjust anticoagulation doses.[42] Clinical pharmacists are licensed practitioners with advanced education and training who practice in all types of patient care settings with a focus on comprehensive medication management.[42] In other words, clinical pharmacists perform functions beyond fundamental dispensing and order-processing activities that are often associated with staff pharmacists.

In developed countries, clinical pharmacists have good knowledge of pharmaceutical products including pharmacokinetics and pharmacodynamics of drug action, drug interactions, and adverse effects and therefore are professionally qualified to manage anticoagulant prescriptions within defined treatment protocols.[43] There are many warfarin clinical–pharmacist-run anticoagulation clinics which have achieved outcomes at a level consistently exceeding INR readings in therapeutic target range and time in therapeutic range.[44,45] Indeed, clinical pharmacists could significantly increase patient access to professional advice and testing, leading to improved INR control and self-care.[46,47] In Africa, there is a paucity of clinical pharmacists trained in anticoagulation management service.

Clinical or specialist nurse-run anticoagulation clinics are also common in developed countries. They are knowledgeable in the science and practice of anticoagulation and can provide services that can enable the patient benefit from the lifesaving effect of anticoagulants by improving the time within therapeutic range whilst reducing the risk of complications. They are capable of educating the patient and creating the relationship that will help improve compliance to anticoagulants.[48]

In Africa, there are probably few clinical pharmacists and nurses in the same mode as obtains in USA. A pilot study to find the effect of clinical pharmacist intervention in Ahmed Gasim cardiac surgery and renal transplant center warfarin clinic in Sudan showed a significant ($P < 0.01$) improvement in INR control and a significant ($P < 0.05$) reduction in incidence of bleeding after clinical pharmacist intervention.[49] Hospitalization due to warfarin related complications (bleeding, high INR, low INR) was also significantly ($P < 0.001$) reduced. Hence, clinical pharmacists' intervention in warfarin therapy even in Africa can improve INR control and reduce bleeding and hospitalization due to warfarin complications. This shows that the type of outcome seen in developed countries can be obtained in Africa if clinical pharmacists are available.

Anticoagulation structure is poorly developed in Africa. There are no anticoagulation services in primary and secondary hospitals and there is only limited number in most tertiary hospitals. In most hospitals in Africa, patients get anticoagulation prescription with little or no monitoring. The few anticoagulation management services are domiciled in tertiary hospitals where physicians work. This type of structure has made anticoagulation available to only the few lucky patients leaving the majority with a tremendous burden of thrombotic diseases.

However, with a proper anticoagulation policy, physicians working together with the right staff-mixture can deliver accepted anticoagulation service. Multiprofessional anticoagulation management service brings physicians, pharmacists, nurses, and dieticians in one clinic to deliver service. This type of service is ideal in tertiary hospitals where physicians can diagnose thrombotic diseases, prescribe anticoagulants, and the pharmacists and nurses take over the follow-up and refilling of anticoagulants. All complications arising from anticoagulation are managed by the physicians. This type of multiprofessional collaboration has been shown to improve efficacy of anticoagulants and reduce costs in Africa, Asia, Europe, and USA.[50-52] Cardiologists and hematologists have often been the physicians who drive this type of institutionalized anticoagulation management service.

Anticoagulation management in the era of NOAC

It had seemed that with the advent of NOACs the anticoagulation management service will be dismantled. This thinking is borne out of the belief that NOAC is given orally, does not require monitoring, has limited drug interaction, and has reduced adverse effects. There are some changes that should accompany management of NOACs so as to fit into already existing VKA clinics. The differences between VKA clinics and NOACs clinics are depicted in Table 3. The clinics are meant to run concurrently and so suitable adjustments are required.

The service for patients on NOACs will require proper documentation just as in warfarin therapy though with some adjustment in protocol. Drug–drug and drug–food interactions may be greatly limited with NOAC in comparison with warfarin but there are reasons to tread cautiously. Patients who are on NOAC and need surgery or a medical procedure[53] or have renal impairment will need adjustment of therapy.[23]

In the new era of NOAC, it is important to strengthen anticoagulation management service infrastructure in African countries. There has to be an anticoagulation policy that should birth anticoagulation services. Anticoagulation services incorporating NOACs should aim to (1) to assist patients and clinicians with selecting the most appropriate drug and dose from a growing list of anticoagulant options (including warfarin), (2) to help patients minimize the risk of serious bleeding complications with careful long-term monitoring and periprocedural management, and (3) to encourage ongoing adherence to these life-saving medications.[54]

This service should be driven by specialist physicians who are knowledgeable in the principles and practice of anticoagulation. Cardiologists and hematologists seem to be better trained to initiate and carry through this call. All the models of anticoagulation management service can be practiced successfully in Africa. The multiprofessional model, the clinical pharmacist model, the nurse model can be adapted to fit any hospital in Africa. The cardiologists and hematologists together with pharmacists and nurses who constitute multiprofessional unit are located in tertiary hospitals. The staff pharmacist and nurses and primary care physicians could be trained to do follow-ups in secondary and primary health care centers. This is possible with training that must ensure seamless education geared toward providing efficacious, safe and affordable anticoagulation.

The cardiologists and hematologists who are primary drivers must have access to the latest data and expert opinion via colleagues, academic literature, and internal and external meetings and congresses. They should be able to develop simple flowcharts outlining recommended indications, dose adjustment and follow-up. In addition they must provide education to other hospital departments and primary care doctors on treatment options for VTE/AF; provide education and training to anticoagulation clinic nurses (at least 6-monthly updates) regular updates). Very importantly they are also expected to guide the education of the patient about their condition and how it will be managed.[51,54]

The multiprofessional unit assess all patients needing anticoagulation and does basic laboratory tests.[23,53] Renal function tests (RFTs) are important because all NOACs are excreted to varying degrees by the kidneys with dabigatran being the highest. Renal impairment is determined according to creatinine clearance as calculated using the Cockroft and Gault formula and not the estimated glomerular filtration rate because it does not consider muscle mass. If CrCl is 30–60 ml/min, >75 years or fragile, then 6 monthly RFT is repeated. If CrCl is 15–30 ml/min, 3 monthly RFT is done.

Liver function test is done as well and repeated if there are intercurrent conditions that may impact anticoagulation.

Deranged function will affect anticoagulation.[53] Hemoglobin level and blood group are also done as a baseline tests.[53]

Generic and specific coagulation assays (activated partial thromboplastin time or dilute thrombin time) for dabigatran, and prothrombin or anti-Factor Xa assays for direct Factor Xa inhibitors may be done and repeated in cases of emergency.[23,53] Table 4 outlines the actions to take in clinical conditions during use of NOACs.

Documentation of all current drugs the patient is on is important in order to address possible drug interaction.[23,53] All 4 NOACs interact with the P-gp transporter and all but dabigatran interact with CYP3A4.[54-58]

Strong inhibitors of P-gp and CYP3A4 include amiodarone (only for dabigatran), quinidine verapamin, azithromycin, clarithromycin, erythromycin, the fungal zoles (itraconazole, ketoconazole, posaconazole, voriconazole: only for dabigatran), HIV protease inhibitors (lopinavir, ritonavir, indinavir: not for dabigatran), immunosuppressants (Ciclosporin, Tacrolimus: only for dabigatran). These drugs should be avoided when NOAC is used or in cases of overriding co-administration or reduced renal function (CrCl 30–50 mL/min), reduce dose to half.

Strong inducers of P-gp and CYP3A4 include Carbamazepine, Phenobarbital (not with dabigatran), Phenytoin, Primidone, Rifampicin, St John's Wort (not with dabigatran). Avoid co-administration with NOAC or use with reduce dose in clinical conditions that indicate overriding use of NOAC.

Every patient on NOAC should have an anticoagulation card with full name and address of the patient, clear indication of the reason for anticoagulation, the type and dose of anticoagulant, time of intake, with or without food, when treatment was initiated, the name, phone number and address of the anticoagulation coordinator.

Patient should be well educated on the basic knowledge of their condition, treatment, desired period of anticoagulation, awareness of what to do if an adverse event occurs, and ability to differentiate between minor and major events. All possible drug–drug interactions should be explained to the patient and the patient should inform the health care giver whenever there is need to buy over the counter drugs. Patients should maintain regular contact with the supervising health care giver who is responsible for follow-up at a frequency dependent on individual risk assessment.

Patients on NOAC will need to understand that adherence is key to successful anticoagulation. Documentation of adherence is absolutely necessary. With shorter half-lives than warfarin, adherence to the NOACs is essential.

The frequency of monitoring will vary. Evaluation at the time of initiation of therapy is important, during surgery or any procedure will be required. Follow-up will be required within 1 month, 3 months, 6 months following initiation of therapy; at the time of dose adjustment higher or lower.[59]

The challenge of coping with anticoagulation management in the era of NOAC in Africa

The very important challenge to the use of NOAC in Africa and other developing countries is the high out of pocket

Table 4: Depicting the action to take in clinical conditions associated with management of non-Vitamin K antagonist oral anticoagulants[59]

Clinical condition	Action to take
When switching from warfarin to a NOAC	The NOAC should be started when the INR is <2.5
When switching from a NOAC to warfarin	Warfarin should be started and the NOAC continued until the INR is ≥2. Repeat the INR 1-3 days after stopping NOAC to ensure INR remains therapeutic
For nonlife-threatening major bleeding event	Plasma levels of NOACs should normalize within 12-24 h for patients with normal renal function. It may take longer for patients with renal insufficiency, particularly for dabigatran
For life-threatening major bleeding event	Patients on dabigatran can be given idarucizumab 5 mg IV in two doses no more than 15 min apart
	Patients taking factor Xa inhibitors should be given prothrombin complex concentrate 50 U/kg
	All patients should receive supportive measures, including mechanical compression and endoscopic or surgical hemostasis (if applicable)
Following a major gastrointestinal bleeding event	NOACs should be restarted as early as feasible (usually 4-7 days) if the risk of stroke persists and outweighs the risk of recurrent bleeding
Surgery and procedures	Most patients taking NOACs can safely undergo surgical procedures with a 24-48 h preprocedure hold
	Longer hold times may be necessary for patients taking dabigatran who have chronic kidney disease. No bridging heparin is needed for NOAC-treated patients. Resume full-dose NOAC within 72 h postprocedure, once the bleeding risk is appropriate
Acute coronary syndrome needing intervention	For patients taking NOAC who present with an acute coronary syndrome, primary PCI can be performed (preferably using a radial approach) emergently for STEMI patients or delayed for 24-48 h in stable NSTEMI patients. Consider a proton pump inhibitor for patients taking combined NOAC with antiplatelet medications
Acute ischemic stroke	For patients taking NOACs who present with an acute ischemic stroke, consider re-starting NOACs after 3-14 days, depending on the degree of neurologic deficit and excluding any hemorrhagic transformation on brain computed tomography

PCI: Percutaneous coronary intervention, IV: Intravenous, STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non-STEMI, NOACs: Non-Vitamin K antagonist oral anticoagulants, INR: International normalized ratio

expenditure of patients. The health insurance system is very poorly developed in most African countries. In Nigeria for instance there is a health insurance scheme but the coverage is poor. It is also bedeviled with corruption and so does not lift the burden of expenditure from the ordinary citizen. This implies that inspite of the fact that the NOACs have better benefit-risk and cost assessment ratio than warfarin, the average patient sees only the low unit cost of warfarin and so NOAC will continue to be less preferred.

The clinical indications for the use of NOAC will continue to expand as more clinical trials get on the way.[60] The use of NOACs in Africa will leap frog close to levels seen in USA and Europe if (1) The insurance scheme is overhauled and made to run efficiently so that patients can afford the high cost of NOACs. (2) The pharmaceutical companies bring down the cost of their products or if generic drugs are allowed to enter the market and make it more competitive. (3) There are anticoagulation policies that promote the establishment of anticoagulation management services. (4) Anticoagulation services are tailored to meet the peculiar health management system in Africa in such a way that the available staff are retrained to provide the much needed lifesaving service of anticoagulation.

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Conflicts of interest

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