Moving Towards Ideal and Appropriate Models of Anticoagulation Management Service

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Abstract

It is now known that thrombotic disorders such as venous thromboembolism, ischemic stroke, and myocardial infarction contribute significantly to global morbidity and mortality. Anticoagulation service must respond to this new development. Warfarin has continued to provide the backbone for anticoagulation service for decades but with considerable drawbacks. The introduction of nonVitamin K oral anticoagulants (NOACs) has created new challenges. This article seeks to discuss how the establishment of appropriate models of anticoagulation could contain the drawbacks of the old anticoagulants and improve on the compliance, availability, affordability, and accessibility of newer anticoagulants. Successful anticoagulation has always been defined by a scientific balancing of the risk of thrombosis and the complication of hemorrhage. To be able to maintain such optimal anticoagulation requires rational drug prescription (physician factor), institutelization of monitoring of therapy (anticoagulation clinic factor) as well as active participation of patients receiving therapy (patient factor). New models of service can be created out of this triad in a bid to replace the old routine medical care model. New models of anticoagulation service should include appropriately trained professionals such as Physicians, Pharmacists, Clinical Pharmacologists, Nurses, and Laboratory Scientists who are knowledgeable in diagnostic, management, and monitoring of anticoagulation. The different models of anticoagulation service discussed in this article clearly demonstrate the need for restructuring of this life saving service particularly in the era of NOAC. Newer models of care that should provide safe, efficacious, and cost-effective services are needed.

Keywords: Anticoagulants, models of anticoagulation service, nonVitamin K oral anticoagulants, thromboembolic diseases, warfarin

Résumé

On sait maintenant que les troubles thrombotiques tels que la thromboembolie veineuse, l’accident vasculaire cérébral ischémique et l’infarctus du myocarde contribuent de manière significative à la morbidité et à la mortalité mondiales. Le service d’anticoagulation doit répondre à ce nouveau développement. L’introduction d’anticoagulants oraux sans vitamine K (NOAC) a créé de nouveaux défis. Cet article cherche à discuter de la manière dont la mise en place de modèles appropriés d’anticoagulation pourrait contenir les inconvénients des anciens anticoagulants et améliorer la conformité, la disponibilité, l’abordabilité et l’accessibilité des anticoagulants plus récents. Une anticoagulation réussie a toujours été définie par un équilibre scientifique du risque de thrombosis et de la complication hémorragique. Pour pouvoir maintenir une telle anticoagulation optimale, il faut une prescription rationnelle des médicaments (facteur médecin), une institutionnalisation de la surveillance du traitement (facteur clinique d’anticoagulation) ainsi qu’une participation active des patients recevant un traitement (facteur patient). De nouveaux modèles de service peuvent être créés à partir de cette triade dans le but de remplacer l’ancien modèle de soins médicaux de routine. Les nouveaux modèles de service d’anticoagulation devraient inclure des professionnels dûment formés tels que des médecins, des pharmaciens, des pharmacologues cliniciens, des infirmières et des scientifiques de laboratoire qui sont bien informés en diagnostic, en gestion et en surveillance de l’anticoagulation. Les différents modèles de service d’anticoagulation abordés dans cet article démontrent
INTRODUCTION

Thrombotic disorders are cardiovascular diseases which contribute significantly to global morbidity and mortality.[1-3] Worldwide, thrombotic disorders have been estimated to cause about 1 out of every 4 deaths in 2010, and it is actually the leading cause of death if their contribution as underlying etiology in venous thromboembolism, ischemic stroke, and myocardial infarction is considered.[1,2]

Thrombotic disorders lead to a hypercoagulable state which puts at risk, the blood supply to end organs and set up a cascade of reactions. The hypercoagulable state results from a reduction of natural anticoagulant mechanisms and/or an increase in the function of procoagulant pathways.[4-7] Hypercoagulable states can be inherited, acquired, or a combination of these. Acquired conditions include obesity, pregnancy, surgery, immobilization, cancer and its treatment, myeloproliferative disorders, heparin-induced thrombocytopenia, estrogen therapy, and history of prior thrombosis.[4-7] Inherited hypercoagulable conditions include deficiencies of antithrombin III, protein C, or protein S, presence of anticardiolipin antibody, lupus anticoagulant, factor V Leiden mutation.[4-7]

Some of the main clinical states associated with thrombosis include atrial fibrillation, deep vein thrombosis, pulmonary embolism, mechanical heart valves, ischemic heart disease, and dilated poorly contractile hearts.

Thrombosis presents clinically as obstruction to blood flow locally or distally if embolism occurs and leads to end-organ damage. Antithrombotic agents are available to manage disease conditions arising from thrombosis. Anticoagulants that are useful in the management of thrombosis are invaluable in anticoagulation service. With the increase in the prevalence and incidence of thrombotic disorders, there has been an upsiding of demand for anticoagulation services. In the past decade, new anticoagulants have been introduced. All these have presented unprecedented demands for restructuring of anticoagulation services. This article examines the staff profiles, the working structure, the determinants of choice of anticoagulation model, and theorizes the nature of an ideal anticoagulation service.

THROMBOSIS AND ANTICOAGULANTS

Thrombosis is conventionally divided into arterial and venous.[1] This division tends to put intracardiac thrombosis in a classless state. A more pathophysiologically oriented classification will have arterial, venous, and cardiac thrombosis subclasses as depicted in Table 1.[10] This type of classification will be useful in coupling the underlying pathophysiology to antithrombotic agents that are indicated. The therapy of arterial thrombosis will require antiplatelets while that of venous thrombosis, anticoagulants; cardiac thrombosis, antiplatelets anticoagulants or a combination of these depending on the underlying overriding or predominant pathophysiology.

Anticoagulants can be divided into parenteral and oral groups. Some parenteral anticoagulants require plasma cofactors, for example, antithrombin III to mediate their activity and some do not. This forms the basis of classification into indirect acting (needing antithrombin) and direct acting (not needing antithrombin).[10] The direct-acting tissue-specific parenteral anticoagulants are: Hirudin, bivalirudin, and argatroban and the indirect-acting non-tissue specific are: unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), fondaparinux, and danaparoid.[10-12]

UFH which is indirect acting, binds to antithrombin via a unique pentasaccharide sequence and catalyzes the inactivation of factors II, VII, IX, and X. LMWH binds more to factor Xa than factor II.[11,12] LMWH have more predictable pharmacokinetic and pharmacodynamic properties because of this as well as its less binding to cells and plasma proteins. The remarkable clinical usefulness of LMWH comes from once to twice daily subcutaneous administrations, no coagulation monitoring and reduced nonhemorrhagic side effects.[11,12] Fondaparinux is another indirect-acting parenteral agent that is an antithrombin-mediated factor Xa inhibitor. It has reduced side effects and does not cause heparin-induced thrombocytopenia which is one of the side effects of UFH.[13] Hirudin is an irreversible factor II inhibitor replaced by a synthetic analog, bivalirudin, which is now used in
percutaneous coronary interventions because of its short half-life.\textsuperscript{[14]} It is also used in the management of HIT. Argatroban is a synthetic reversible direct factor II inhibitor.\textsuperscript{[15]} It is also used in patients with HIT and can be monitored using activated partial thromboplastin time.

The oral anticoagulants can likewise be divided into direct-acting tissue-specific (dabigatran, rivaroxaban, apixaban, and edoxaban) and indirect-acting nontissue specific (warfarin) subgroups.\textsuperscript{[16]} The indirect-acting anticoagulants or Vitamin K antagonists inhibit γ-carboxylation of factors II, VII, IX, and X which requires Vitamin K to occur.\textsuperscript{[10]} Treatment with Vitamin K antagonists results in the hepatic production of partially carboxylated and decarboxylated proteins with reduced coagulant activity.\textsuperscript{[10]} Warfarin is the most commonly used Vitamin K antagonists; acenocoumarol is less commonly used.\textsuperscript{[16]} Although Vitamin K antagonists are absorbed quickly their full effect develops after about 5 days when the activity of all Vitamin K-dependent coagulation factors is reduced.\textsuperscript{[16]}

Warfarin has been in existence for more than 60 years before the introduction of direct-acting oral anticoagulants. Dabigatran, a direct factor II inhibitor was approved in 2010,\textsuperscript{[17]} rivaroxaban, a direct factor X\textsubscript{i} inhibitor in 2011\textsuperscript{[18]} and apixaban, another direct factor X\textsubscript{i} inhibitor in 2012.\textsuperscript{[19]} Edoxaban was approved in 2015.\textsuperscript{[20]} Inhibition of factor II and factor X eventually leads to decreased thrombin generation, and therefore, a reduction in thrombus formation and progression.

FROM WARFARIN TO NONVITAMIN K ANTICOAGULANTS

Anticoagulants have been used to treat procoagulant conditions aiming to prevent and manage thrombotic states and possible embolic disorders while preventing bleeding, the most feared complication. Successful anticoagulation has always been defined by a scientific balancing of the risk of thrombosis and the risk of hemorrhage. To be able to maintain such optimal anticoagulation requires rational drug prescription (physician factor), institutelization of monitoring of therapy anticoagulation clinic factor) as well as the active participation of patients receiving therapy (patient factor). The physician and patient factors are very well defined. The anticoagulation clinic factor has been fairly well established for warfarin but with the advent of the nonVitamin K oral anticoagulants (NOACs) many are asking the role these anticoagulation clinics should play now.

Warfarin is the oldest anticoagulant haven transited from a rodenticide to approval as an anticoagulant fit for human use.\textsuperscript{[21]} The pharmacokinetics and pharmacodynamics of warfarin is associated with unique anticoagulant properties as well as clinical challenges.\textsuperscript{[29]} The clinical challenges related to warfarin associated drug–drug interaction (DDI), drug-food interaction, drug-disease interaction and aging\textsuperscript{[22]} Other contributors to this scenario include poor drug compliance, dosage error, and laboratory errors. These give rise to adverse effects, all of which may cause considerable morbidity and mortality.\textsuperscript{[6]} These adverse effects, particularly excessive bleeding, had created a deep concern and sometimes feared among physicians who use warfarin leading to its under-prescription.\textsuperscript{[22]}

However, the benefits of the appropriate use of warfarin far outweigh the risk of bleeding and other adverse effects. Indeed, it has been documented that warfarin prevents 20 strokes for every bleeding episode it causes.\textsuperscript{[23,24]}

The availability of NOACs provided confidence for doctors prescribing anticoagulants and was good news for patients needing anticoagulation because no laboratory monitoring was required, the half-life was shorter, making bridging therapy not necessary and anticoagulation effect was possible within hours. The use of NOACs also reduced drug–drug and drug-disease interaction.\textsuperscript{[25]}

However, in spite of the fact that there are sufficient data that guarantee the efficacy and safety of these drugs when given in fixed doses, their use in underweight and obese patients, in patients with bleeding/thrombotic complications where it is necessary to correlate between events and over-/undertreatment and in patients with renal impairment and potential drug–drug and drug-disease interactions exposes the unmet need for some form of monitoring.\textsuperscript{[25]} Anticoagulation clinic is the only set up that will be in a position to manage these challenges and document appropriately the clinical complexities as well as any pharmacovigilance issues. Table 2 outlines anticoagulants, laboratory monitoring, noncoagulation laboratory monitoring, and clinical monitoring.\textsuperscript{[12]}

ANTICOAGULATION SERVICE: WHAT IS NEW WHAT HAS REMAINED UNCHANGED AND RELEVANT?

The availability of NOAC has meant that newly diagnosed patients could get the prescription ab initio if it is the preferred option after consideration of the alternatives. Patients who, despite adequate adherence, spend <65% of the time in therapeutic range (TTR), indicating suboptimal anticoagulant control. Patients with allergic reactions or intolerance to warfarin and patients who have genuine difficulty in attending for INR monitoring will need a switch to NOAC.\textsuperscript{[26,27]}

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 atrial fibrillation, with rivaroxaban being the most frequently prescribed DOAC (47.9%), followed by apixaban (26.5%), and dabigatran (25.5%).\textsuperscript{[26,27]}

The use of NOAC has continued to increase and by 2014 had reached 15.5% globally. On the other hand, warfarin use has declined from 87.5% to 72% to 2008–2014.\textsuperscript{[28]}

In 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.\textsuperscript{[10,11]} About 10% of the volume of service by these clinics are due to patients on NOACs.\textsuperscript{[11]} This proportion will increase as more patients are placed on NOACs.\textsuperscript{[28]}
Data on NOAC in Africa is sparse. The NOAC is relatively new in Africa even though dabigatran, the first NOAC has been in use since 2010. Approvals for NOAC in Africa started in 2011 and dabigatran and rivaroxaban are now widely in use in Namibia, Kenya, South Africa, Nigeria, Uganda and other countries. Notably, 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. Second, Africans have a disproportionately higher number of subjects with valvular (rheumatic) atrial fibrillation in whom NOAC is not indicated. Third, the higher cost, compared to warfarin, will ensure that a greater number of Africans will be excluded from the global market share of NOAC. Fourthly, the knowledge gap and poor anticoagulation management infrastructure have made the use of NOAC to lag behind that of developed countries.

There are a number of reasons to predict that for Africa, the use of NOAC will never catch up with their increasing use in developed countries. First, it should be noted that the use of NOAC has not been well validated in African subjects. Notably, 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. Second, Africans have a disproportionately high number of subjects with valvular (rheumatic) atrial fibrillation in whom NOAC is not indicated. Third, the higher cost, compared to warfarin, will ensure that a greater number of Africans will be excluded from the global market share of NOAC. Fourthly, the knowledge gap and poor anticoagulation management infrastructure have made the use of NOAC to lag behind that of developed countries.

The service for patients on NOACs will require proper documentation just as in warfarin therapy though with some adjustment in the 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 [35] (Tables 3 and 4) or have renal impairment will need adjustment of therapy [36].

### Table 2: Anticoagulants, their laboratory monitoring, noncoagulation laboratory monitoring, and clinical monitoring

| Anticoagulant | Laboratory monitoring for coagulation efficacy and toxicity with (comments) | Noncoagulation laboratory monitoring | Clinical monitoring |
|---------------|--------------------------------------------------------------------------------|-------------------------------------|---------------------|
| Warfarin      | INR, APTT and a platelet count (to screen for underlying coagulation disorders and to establish baseline values. A second sample for INR should then be taken 2-3 days after the initiation of therapy, then two or three times a week and then weekly until stable) | Serum creatinine, liver function tests, and complete | Monitoring using INR should be done not less than 2 weeks to one month until targeted INR is achieved. All drug-drug, drug-disease and drug-food interactions should be monitored. Evidence of overcoagulation (bleeding) and under coagulation (thrombi formation) should be documented |

NOAC

| Activated partial thromboplastin time, prothrombin time, and thrombin time (provides qualitative monitoring) | Serum creatinine, liver function tests, and CBC | Monitoring should be 1-3 months after initiation and then at least every 6 months, with more frequent follow-up (i.e., 3 months) based on patient specific characteristics such as age, renal impairment, hepatic impairment, and concomitant drug therapy |

Parenteral anticoagulants (UFC)

| aPTT and anti-Xa assay | CBC. Monitor platelet count at least every 2-3 days from day 4 to 14 or until UFH is stopped to prevent or identify patients at risk of HIT | Bridging therapy with other anticoagulants should follow guidelines |

Parenteral anticoagulants (LMWH)

| Anti-Xa LMWH | CBC and serum creatinine and consider renal function when using LMWH due to its renal metabolism. An alternative agent or reduced dose should be used if the creatinine clearance is stable) | Bridging therapy with other anticoagulants should follow guidelines |

APTT=Activated partial thromboplastin time, LMWH=Low-molecular-weight heparins, UFH=Unfractionated heparin, INR=International normalized ratio, CBC=Complete blood counts, NOAC=Nonvitamin K oral anticoagulants, HIT=Heparin-induced thrombocytopenia

### Table 3: Preprocedural planning for the direct oral anticoagulants

| DRUG       | Preprocedure renal function | Minor surgery or Standard bleed risk surgery | Major surgery or high bleed risk surgery |
|------------|-----------------------------|--------------------------------------------|----------------------------------------|
| Apixaban   | Serc<1.5 mg/Dl               | Stop 24 h before procedure                  | Stop 48 h before procedure              |
|            | Serc>1.5 mg/dL               | Stop 48 h before procedure                  | Stop 72 h before procedure              |
| Dabigatran | CrCl ≥50 mL/min              | Stop 1-2 days before procedure              | Stop 2-4 days before procedure          |
|            | CrCl <50 mL/min              | Stop 3-5 days before procedure              | Stop >5 days before procedure           |
| Edoxaban   | CrCl ≥50 mL/min              | Stop 24 h before procedure                  | Stop 48 h before procedure              |
|            | CrCl <50 mL/min              | Stop 48 h before procedure                  | Stop 72 h before procedure              |
| Rivaroxaban| CrCl ≥30 mL/min              | Stop 24 h before procedure                  | Stop 48 h before procedure              |
|            | CrCl <30 mL/min              | Stop 48 h before procedure                  | Stop 72 h before procedure              |
DDI is not as common as with warfarin but is very important. Dabigatran and edoxaban are substrates for P-glycoprotein (P-gp). Apixaban and rivaroxaban are metabolized by cytochrome P450 enzyme CYP3A4 and are also substrates for P-gp. Strong enzyme inducers will decrease the effectiveness of NOACS and enzyme inhibitors will do the reverse. Table 5 outlines the DDI related to NOAC that must be taken into account.

Since dabigatran and to a lesser extent, rivaroxaban and apixaban are excreted by the kidneys, and drug accumulation can translate into accentuated anticoagulant effects.

Patients with severe renal impairment [Box 1] will require a significantly reduced dose of warfarin to achieve therapeutic INR in comparison to control of normal kidney function. Patients with a CrCl of 30–59 mL/min/1.73 m² will need a 10% lower maintenance dose, while those with levels of <30 mL/min/1.73 m² a 20% lower dose. This may be related to the down-regulation of cytochrome P450 in CKD.

Patients on NOAC will need to understand that adherence is key to successful anticoagulation. Documentation of adherence, DDI s, side effects including adverse effects is absolutely necessary. The frequency of monitoring will vary. Evaluation at the time of initiation of therapy is important, during surgery

| Drug       | Minor surgery or standard bleed risk surgery | Major surgery or high bleed risk surgery | Onset of anticoagulation (h) |
|------------|---------------------------------------------|----------------------------------------|------------------------------|
| Apixaban   | Within 24 h if approved by surgeon          | Within 72 h if approved by surgeon     | 3-5                          |
| Dabigatran | Within 24 h if approved by surgeon          | Within 72 h if approved by surgeon     | 2                            |
| Edoxaban   | Within 24 h if approved by surgeon          | Within 72 h if approved by surgeon     | 2                            |
| Rivaroxaban| Within 24 h if approved by surgeon          | Within 72 h if approved by surgeon     | 2-4                          |

**Table 4: Postprocedural planning for the direct oral anticoagulants**

| Drug       | Minor surgery or standard bleed risk surgery | Major surgery or high bleed risk surgery | Onset of anticoagulation (h) |
|------------|---------------------------------------------|----------------------------------------|------------------------------|
| Apixaban   | Within 24 h if approved by surgeon          | Within 72 h if approved by surgeon     | 3-5                          |
| Dabigatran | Within 24 h if approved by surgeon          | Within 72 h if approved by surgeon     | 2                            |
| Edoxaban   | Within 24 h if approved by surgeon          | Within 72 h if approved by surgeon     | 2                            |
| Rivaroxaban| Within 24 h if approved by surgeon          | Within 72 h if approved by surgeon     | 2-4                          |

**Table 5: Drug-drug interactions of non-Vitamin K oral anticoagulants**

| Class                                      | Drugs                                      | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|--------------------------------------------|--------------------------------------------|------------|-------------|----------|----------|
| Strong P-gp inhibitors (also CYP3A4 inhibitors) | Ciclosporin                               | 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                                | 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                             | 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 |
| Others                                    | Aspirin Clopidogrel                        | 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 |
|                                           | NSAID’s                                   | Combination not recommended               | Combination not recommended    | Combination not recommended    | Combination not recommended    |
|                                           | Prasugrel Ticagrelor                      | Combination not recommended               | Combination not recommended    | Combination not recommended    | Combination not recommended    |

LMWH=Low-molecular-weight heparins, UFH=Unfractionated heparin, NSAID=Nonsteroidal anti-inflammatory drug
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.\[25] The focus of this article is on the management of anticoagulation service relating to oral anticoagulants, particularly warfarin and NOACs, but parenteral anticoagulants including indirect anticoagulants, UFH, LMWHs, fondaparinux, and danaparoid, as well as the direct thrombin inhibitors hirudin, bivalirudin, and argatroban have their own clinical indication in the treatment and prophylaxis of thromboembolism. Table 2 outlines anticoagulants, laboratory monitoring, noncoagulation laboratory monitoring, and clinical monitoring.

The parenteral anticoagulants are not usually monitored using laboratory tools. However, for UFH, aPTT and anti-Xa assay are available to aid monitoring to ensure safety and efficacy. The TTR for anti-Xa UFH activity is 0.3–0.7 international units of heparin per milliliter. High values indicate high levels of heparin; low values indicate low levels of heparin.\[10] LMWH is also used for anticoagulation. Anti-Xa LMWH monitoring may be warranted for specific patient conditions: obesity (body mass index >50 kg/m\(^2\)); small stature (<50 kg); impaired renal function (creatinine clearance <30 mL/min); and pregnancy. The anti-Xa laboratory test for LMWH is different from the anti-Xa laboratory test for UFH; target (peak) ranges for anti-Xa LMWH are approximately 0.6–1.0.5.\[10] Warfarin has remained the most prescribed anticoagulant worldwide with the trend gradually changing to NOAC in the high-income countries. Therapeutic monitoring of the anticoagulant effect of warfarin is performed by measuring the prothrombin time (PT). PT is the time, in seconds, taken for blood to clot when mixed with a fixed amount of thromboplastin and calcium. INR is the format of reporting laboratory monitoring of warfarin to help minimize inter-laboratory variation.\[9,16] Clinical indications for anticoagulation have continued to increase and so will the trepidations on the use of anticoagulants.\[9] The challenge in the use of anticoagulants will continue not only in the management of patients that attend tertiary hospitals but also in patients that are seen in the primary and secondary levels of health-care systems where resources for monitoring and the fear of the adverse effects of anticoagulation may be enormous.\[43,44] It is thus important not only to follow established guidelines in anticoagulation but to also institute the necessary infrastructure for practicing established guidelines.\[144,46] This is the reason why clear definition of the models of anticoagulation is important and very useful in the achievement of the goals of anticoagulation.

**Staff Profiling of Anticoagulation Service**

An ideal anticoagulation service provides diagnostic, therapeutic, management, and monitoring functions for patients who have thromboembolic diseases.\[47,48] The provision of anticoagulation service is done by appropriately trained professionals who are knowledgeable in the science and its application of anticoagulants to the management of thromboembolic diseases.\[49] Thromboembolic diseases are basically vascular phenomenon and most cardiologists, hematologist and clinical pharmacologists are trained in the basic science of anticoagulation.\[50] Pharmacists and nurses who have advanced training in cardiovascular medicine could also be knowledgeable enough to offer anticoagulation service.\[51,52] The diagnostic component of the clinic ensures that adequate clinical work is done to enable the appropriate diagnosis of thromboembolic disorder that requires anticoagulation. It presupposes that physicians with the requisite training are available to do the assessment as it will be therapeutic rascality to prescribe anticoagulants for patients without the clinical indication or to do so outside the accepted guidelines.

Generally, cardiologists or hematologists have adequate training to take on assessment roles in any anticoagulation clinic. The physician is thus capable of taking on the diagnostic to the monitoring components but in keeping with job descriptions in the health sector will need a complement of other professionals including clinical pharmacists, clinical pharmacologists, nurses, laboratory scientists, dieticians, and medical records staff.\[50,52] The therapeutic and monitoring aspect of the clinic can be done by the physician but clinical pharmacologists, clinical pharmacists, and nurses have been trained in many centers to perform these roles to provide regular and seamless anticoagulation service.\[51,52] These staff are usually trained to keep to established guidelines for anticoagulation and to collaborate with physicians particularly in diagnosis, complicated therapeutic, and monitoring of anticoagulation.

The pharmacists and nurses have a mainly supportive role in managing adverse effects including moderate to severe bleeding and in bridging therapy as well as anticoagulation therapy during surgery and other procedures.

The monitoring of anticoagulation includes choosing the best template that ensures that the patient is well anticoagulated. In the case of warfarin, it includes using INR to monitor the effectiveness of anticoagulation.\[53] There are no approved tools for monitoring the direct oral anticoagulants for the now.\[54] The laboratory scientists are usually in charge of this aspect of the service, though with the advent of point of source strips virtually anybody from the physicians to the patient can perform this function.\[55] The management aspect of the clinic presupposes that the entire aspect of the clinic function is included but for the sake of the discussion here defines that aspect that deals with under and over anticoagulation. It includes the management of DDIs, drug-food interactions as well as the use of appropriate therapy for managing the clinical conditions associated with thrombosis and bleeding. It is known that undercoagulation will lead to thrombosis with its attendant morbidity and mortality.
multi-staff care (MSC) model. Patients sent to MSC usually able to monitor and adjust anticoagulants, it is called the patient monitoring care (POMC) model. If the patient is able to monitor anticoagulation using point of care strips. This sort of referral is common in developing countries where diagnostic services are not optimal and patients may need clinical workup for diagnosis before anticoagulation. The most common resultant effect of overanticoagulating is bleeding. Physicians (cardiologists and hematologists) are required to provide other services and then are required to manage patients with thromboembolic disorders. The service is given as part of routine medical care (RMC model). The clinical outcome of patients managed in the RMC model has been enormous and so efforts have been made to maximize the services of clinical pharmacologists, clinical pharmacists, and nurses in providing anticoagulation services. The most suited in managing the clinical outcome of under and overanticoagulating. The nurses can be trained to do laboratory monitoring of anticoagulation and prescribe anticoagulants accordingly.

Before administration, the nurse would also check that there are no allergy, contraindication, and interactions. After administration, the nurse would check and monitor for side effects and adverse effects and report any of these to refer team. Patients who are sufficiently trained and motivated are now able to monitor anticoagulation using point of care strips. This is the patient monitoring care (POMC) model. If the patient is able to monitor and adjust anticoagulants, it is called the patient self-management care (PSMC) model. PSMC requires training, motivation, and the use of telemedicine.
adjudged to be a safe, sustainable, and acceptable model of care for individuals with routine anticoagulation monitoring and management needs.\textsuperscript{[31]} It is also said to be effective and safe in a long-term real-life setting and robust across clinical subgroups.\textsuperscript{[67,68]}

MSC can be combined with the CPAC or CPC or NCM or POMC. The MSC assesses the patients, initiates management and the continued care can be provided by other care model. This is ideal for busy centers in low resource countries, in high turnover valvular replacement centers and in developed countries that have a high load of patients requiring anticoagulation or that have a high turnover of valvular replacement surgery cases.

**Determinants of Choice of Anticoagulation Service Model**

Costs as well as the availability of telemedicine and other forms of electronic communication must be considered in the choice of anticoagulation service. In low resource settings, the RMC model is common because it is cheap and does not require any special arrangement to set up as it forms part and parcel of RMC.

The CPC model, CPAC model and NC model require differing forms of communication with the patients to be effective. Patient care models require even more communication tools. The availability of communication tools and computerized applications could change the way anticoagulation service is delivered. Computerized decision support system is now available to provide guidance in warfarin dosing based on INR results.\textsuperscript{[69]} This type of computerized support will ultimately enable other health-care professionals to manage anticoagulation clinics.\textsuperscript{[70]}

The authors’ center is the national cardiothoracic center of excellence in Nigeria and so we have a large pool of patients with valvular replacement. We also cater for the needs of patients who undergo interventional cardiology procedures, patients with degenerative and rheumatic valvular heart disease, severe heart failure with markedly dilated cardiac chambers, and patients with myocardial infarction. We have combined the MSC model with the CPAC model. We are about to also bring in the NC model and the CPAC model to optimize the available staff. The MSC model clinic is on Tuesdays and we have patients referred from our doctor and from other hospitals. The attending physicians have the duty of confirming or making a diagnosis to ensure that patients need anticoagulation. The patients are then assessed clinically and using laboratory tests. After these processes, they are now placed on anticoagulants and given appointment for continued physician management or referred to CPC clinic for continued care and refills. We have encouraged physicians to also send in patients on NOAC for documentation and follow-up. Our experience is that appropriately trained pharmacists, nurses, and clinical pharmacologists appear equally safe and effective as physicians when managing warfarin therapy in patients who need anticoagulation. This is in some ways similar to outcomes in other centers.\textsuperscript{[71,72]}

Hence, the submission is that if the intention is to achieve high quality of clinical service and increase the time within TTR for warfarin therapy then RMC should not be practiced. Other models of care are likely to lead to improved TTR and to lead to clinical and cost-effectiveness, though in varying degrees.\textsuperscript{[73,74]}

Table 6 depicts some of the characteristics of different models of anticoagulation and uses plus, +, to depict the strength of the component of assessment of the models. For instance time within therapeutic range (TTR) is easily achieved in most of the models and so has ++++ to +++++ except routine care model where care is uncoordinated and unsupervised and so has only +.

The traditional anticoagulation service was for warfarin use. Times have changed with the availability of NOACs. The anticoagulation service must now include not just warfarin but NOAC and indeed all anticoagulants and antithrombotics as drugs that should be monitored clinically and ideally with laboratory tests. Table 7 defines some of the differences between a warfarin predominant anticoagulation service and the NOAC predominant service.

NOACs are now widely available and their use has become more prevalent in recent years particularly in high-income countries.\textsuperscript{[75-78]} Cost issues have delayed their full use in

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
\textbf{VARIABLE} & \textbf{RMC} & \textbf{MSC} & \textbf{CPAC/CPC/NC} & \textbf{PC} & \textbf{Combined care} \\
\hline
Clinical quality & + & ++++++ & +++++ & +++++ & +++++ \\
TTR easily achieved & + & +++++ & +++++ & +++++ & + \\
Costs+ telemedicine & + & ++++ & ++++ & ++++ & + \\
Ease of accessing quality care by patients & + & ++++ & ++++ & ++++ & ++++ \\
Commonly found in high resource countries & + & +++++ & ++++ & +++++ & ++++ \\
Commonly found in low resource countries & ++++ & + & + & + & + \\
Appropriate for warfarin therapy & + & ++++ & ++++ & +++++ & ++++ \\
Appropriate for NOAC & + & ++++ & ++++ & ++ & ++ \\
\hline
\end{tabular}
\caption{Characteristics of models of anticoagulation service}
\end{table}
low-income countries. There is still the fear of reversibility and also bleeding and how to manage it as well.[79]

However, there is the argument that warfarin is only cheaper in outpatient care that is not complicated by bleeding complications. However in real terms the total cost of inpatient admissions, in the Warfarin group is higher than the DOAC’s, leading to considering DOAC’s as a cost-effective alternative to Warfarin in this scenario.[79]

It is logical to think that the markedly reduced drug–drug and drug-food interaction and the disabling of laboratory monitoring of NOAC may reduce the utility of the multi staffed clinic model for NOAC. However, there is a caveat in this proposition. NOAC are new drugs and there is a need for continued monitoring and pharmacovigilance and hence, it is very important that physicians supervise the use of these drugs until sufficient data has been gathered as was done for warfarin.

Certainly NOAC is not appropriate for the patient models of service. The patient models have no way of monitoring patient compliance of the use of NOAC or their efficacy. Centers practicing the CPC model, CPAC model and NC model would need retraining to ensure appropriate documentation in the use of DOAC.

**Conclusion**

The different models of anticoagulation services discussed in this article clearly demonstrate that this life-saving service can be used in varying situations irrespective of income level, cultural, and social conditions and not minding whether it is the primary, secondary, or tertiary level of healthcare. The availability of well-validated INR machines together with computer-guided program, could ultimately bring warfarin-based anticoagulation service to every patient that needs it.[80]

The widespread use of NOACs, however, will need some form of control until monitoring tests are available, affordable, and easily accessible. Anticoagulation services will continue to evolve until an ideal state when the service is available anywhere, anytime with adequate monitoring to ensure efficacy, safety, convenience, and minimal adverse effects.

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