CURRENT APPROACHES TO PREVENTION OF VENOUS THROMBOEMBOLISM FOLLOWING MAJOR ORTHOPAEDIC SURGERY: A REVIEW OF RECOMMENDATIONS BY INTERNATIONAL GUIDELINES

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ABSTRACT

Objectives: Venous Thromboembolism (VTE) is an important cause of morbidity and mortality amongst patients who undergo major orthopaedic surgical procedures. The perioperative use of thrombo-prophylactic agents with or without mechanical compression has demonstrated significant lowering of the incidence of VTE among post-operative patients. Various pharmacological and mechanical agents are available locally in both oral and injection forms but there are no standard guidelines or a consensus statement on their utilization. This is the case despite there being a gradual rise in the number of patients who undergo hip and knee replacement surgery in Kenya. The purpose of this paper is to review the current approaches being used to reduce post hip and knee replacement incidences of VTE as recommended by various external guidelines for benchmarking purposes in the Kenyan context.
Data Sources: This article relies on published scientific data from various online resources including journals and electronic databases.
Data selection and extraction: The data that is cited in this article has been referenced from health publications that are available online through internet literature search and googling Cochrane review, Pub Med, MedScape and Medline websites.
Conclusions: The use of mechanical and pharmacological methods to prevent VTE following major orthopaedic surgery is recommended and practiced worldwide. The choice of the prophylactic regimes should be adapted to patient needs taking into consideration their risk profiles for bleeding and development of VTE as well as the availability and access to the prophylactic treatment. Several countries have developed VTE prevention guidelines in line with international practice and adapted them to their local situations. In the Kenyan context a gap remains for development of local VTE prevention guidelines that will inform and enable clinicians to make rationale choices while selecting appropriate VTE prevention measures.

INTRODUCTION

Pathophysiology of VTE: The coagulation pathway is influenced by a balance of various factors that maintain a physiologic equilibrium that controls clotting and bleeding which when disrupted may lead to hypercoagulation or excessive bleeding. Virchow's triad describes three critical conditions that are important for the development of thrombosis i.e. circulation stasis, endothelial or blood vessel wall damage or dysfunction and hyper-coagulation states (1). Thrombus formation may be initiated via several physiological pathways consisting of activation of enzymes that magnify the effect of an initial trigger event. A similar complex of events results in the dissolution of the clot leading to equilibrium between the two mechanisms. Microscopic thrombus formation and their dissolution are continuous events but with increased stasis, pro-coagulant factors or endothelial injury the coagulation-fibrinolysis balance

may favor the formation of an obstructive thrombus (2). Thrombosis following orthopaedic surgery may be contributed to by multiple factors including prolonged immobilization during and after surgery leading to stasis, intrinsic or extrinsic blood vessel wall injury and post-operative hypercoagulable states arising from increased circulating tissue activation factors and reduced plasma antithrombins such as heparin-antithrombin 111 (AT111) and fibrinolysins. Studies have demonstrated that levels of circulating AT111 are decreased more and stay reduced longer after total hip replacement than after general surgical cases (2).

Aetiology, presentation and complications of VTE: VTE is a serious complication that develops amongst hospitalized patients and those who have undergone major orthopaedic surgical procedures such as Total Hip Replacement (THR), Total Knee Replacement (TKR)

and Hip Fracture Surgery (HFS). In addition to patient specific risk factors surgical patients are at risk of VTE as a consequence of the surgical procedure itself, the type of anaesthetic used, the presence of infection, and the extent of postoperative immobilization (3). Subsequently, without any form of prophylaxis over half of the patients who undergo total hip or knee replacement develop Deep Venous Thrombosis (DVT) as shown by studies using postoperative venography, and between 7 and 11% have lung scans which show a high probability of pulmonary embolism within 7-14 days after surgery (3). Approximately 50-80% of cases of deep venous thrombosis are asymptomatic and more than 70% of PE go undetected until a postmortem examination is performed after sudden death which is often the first sign of PE (4) hence the common reference to DVT as a silent killer.

Up to 40-60% of patients that undergo orthopaedic surgery develop asymptomatic VTE which can be detected by venography when no prophylaxis is administered (4). When thromboprophylaxis is used 1-10% of patients develop VTE within 3 months after surgery (4). VTE may complicate to Pulmonary Embolism (PE) or post-thrombotic syndrome which is characterized by swelling of the affected limb, pain, purpura, dermatitis, ulceration, pruritus and cellulitis which may further necessitate amputation of the limb impacting significantly on the patient's quality of life. Patients with DVT may not seek medical attention, and less than half of all fatal pulmonary embolism cases are detected before death (5).

The risk of DVT may persist for up to 2 months after total hip replacement whereas symptomatic VTE has been documented at 90 days in patients undergoing total hip or knee replacement (6). In patients who have undergone hip or knee arthroplasty, the majority of thromboembolic events occur after discharge from hospital (6). Even where thromboprophylaxis has been used the occurrence of DVT has been documented at

the rate of 2.8% among patients who have undergone THR and 2.1% in those who have undergone TKR within three months of surgery (7). Apart from reducing the incidences of DVT the prevention of fatal PE is generally expected and forms the main basis of thromboprophylaxis in orthopaedic surgery. However there is conflicting interpretation of the available evidence as to whether actual reduction in PE is achieved through thromboprophylaxis even when DVT rates are reduced. The American Association of Orthopaedic Surgeons (AAOS) guidelines on prevention of DVT among patients undergoing major orthopaedic surgery do not consider symptomatic and asymptomatic DVT as surrogate markers for PE citing lack of evidence linking them (8). The American College of Chest Physicians (ACCP) guidelines on DVT prevention in orthopaedic surgery on the other hand have included venographic evidence of DVT as a measure of the efficacy of thromboprophylaxis (9). Both guidelines compared evidence from various clinical trials data and arrived at different conclusions therefore creating two conflicting views. Further and wider consultations need to be initiated amongst clinicians to build up consensus on this subject.

DISCUSSION

Assessment for the risk of post-operative DVT and bleeding: When using anticoagulation therapy amongst patients undergoing major orthopaedic surgery the risk of major postoperative bleeding must be balanced against the benefit of preventing thrombosis. Several DVT prophylaxis treatment guidelines recognize and acknowledge the practice of assessing the risk of DVT development versus bleeding amongst patients undergoing hip and knee replacement surgery. However there are no standardized DVT risk assessment criteria hence various guidelines have made recommendations that overlap as indicated in Table 1.

Table 1
Pre-operative VTE risk factors assessment as recommended by ACCP, NICE and SA guidelines

Guidelines	VTE risk factors
ACCP	Major surgery
	Previous VTE, Cardiovascular disease, Charleston co-morbidity index ≥ 3, Obesity (BMI ≥ 25)
	Age (increases every 5 years after 40 years)
	Advanced age (> 85 years)
	Varicose veins
	Ambulation before day 2 after surgery
National Institute of Clinical Excellence	Surgery with procedure > 60 mins
	Expected significant reduction in mobility
	One or more of the following: Active cancer or cancer therapy, Age> 60 years, dehydration, critical care admission, Known thrombophilia, obesity (BMI > 30), significant medical co-morbidities, personal or first degree relative history of DVT, use of hormonal replacement therapy, use of oestrogen therapy, varicose veins with phlebitis, inflammatory bowel disease
South African Society of Thrombosis & Haemostasis	History of VTE (H), extent of tissue damage (H) degree of immobility following surgery(H), underlying malignancy (H), hereditary thrombophilia(H), HIV/AIDS(H), Autoimmune diseases(H), duration of surgery(H), Age >60 years(M), obesity(M), estrogen therapy(M), pregnancy and postpartum period (L), Nephrotic syndrome (L), Varicose veins (L), inflammatory bowel disease

Although individual VTE risk factor assessment carries considerable appeal it is limited by lack of validation in orthopaedic surgery (8). Other risk factors for development of VTE include indwelling central venous catheter, chronic respiratory failure, hyper-viscosity, hyperlypidemia, paralytic stroke and use of various medicinal products (6). Inherited factors such as functional deficiencies of inhibitors of coagulation factors (antithrombin, protein S, and protein c), mutation in prothrombin gene, increased concentrations of homocysteine and Factor V mutation may also predispose to the development of DVT (6). The AAOS guidelines are equivocal regarding whether to use any other criteria for DVT risk assessment in major orthopaedic surgery patients other than history of previous DVT. This is based on the understanding that these patients are already at high risk of developing DVT and there is limited evidence on the benefits of such routine screening (8). The ACCP concur that for major orthopaedic procedures the surgery specific risk for DVT formation far outweighs the contribution of the patient specific factors (9). Both the National Institute for Health and Clinical Excellence (NICE) guidelines (10) and the South African Society of Thrombosis and Haemostasis guidelines (11) agree on the need for pre-operative DVT risk assessment before considering prophylactic treatment options which should be adjusted according to the individual patient needs. The South African guidelines further stratify the DVT risk factors as High (H), Moderate (M) and Low (L) as indicated in Table 1.

General risk factors for bleeding after hip and knee arthoplasty include previous major bleeding, severe renal failure, concomitant antiplatelet agent use and surgical factors such as history of or difficult to control surgical bleeding during the current operative procedure, extensive surgical dissection and revision surgery (8). Bleeding could occur generally and in severe cases it can lead to depleted plasma volume which is occasionally life threatening. At the operation site bleeding can complicate to joint stiffness through formation of a haematoma which may also lead to infection and compromise the functional outcome of the procedure. No bleeding risk assessments have been sufficiently validated in the orthopaedic surgery population hence specific thresholds for using mechanical compression devices or no prophylaxis instead of antiocoagulant thromboprophylaxis have not been established (8). The AAOS evaluated six studies among non arthroplasty surgical patients in which bleeding time predicted blood loss in one of three studies, fibrinogen predicted blood loss in one of three studies, platelet count predicted blood loss in one of six studies and prothrombin time predicted blood loss in one of six studies. Nevertheless the AAOS recommends that owing to the increased risk of bleeding and bleeding associated complications and in the absence of reliable evidence patients undergoing elective hip and knee surgery should be assessed for known bleeding disorders such as haemophilia and for the presence of active liver disease which further increase the risk of bleeding and its associated complications. However clinicians need to be aware of the established contraindications against the use of individual anticoagulant agents (8).

Measures for prevention of DVT among patients undergoing TKR and THR: Globally several guidelines and consensus statements for prevention of VTE in patients undergoing orthopaedic surgery have been developed. For bench marking purposes this review will focus on guidelines as recommended by the ACCP, NICE and the South African Society of Thrombosis and Haemostasis (9-11) as outlined in Table 2.

Mechanical methods of thromboprophylaxis: Various mechanical methods of thromboprophylaxis are recommended by the ACCP, NICE and S. African guidelines. These methods include the use of Intermittent Pneumatic Compression Devices (IPCD), Foot Impulse Devices, Venous Foot Pump (VFP), Electrical stimulation and Graduated Compression Stockings (GCS). Mechanical approaches to perioperative thromboprophylaxis with pneumatic compression devices have the potential advantage of reducing the incidence of VTE but without the risk of increased bleeding (9). GCS normally exert pressure on the legs increasing the blood velocity and improving venous return while the IPCD require the intermittent deflation and inflation of garments wrapped around the legs which enhances venous return, prevents venous stasis and stimulates local fibrinolysis (12). The venous foot pump or foot impulse devices use a weight bearing pumping mechanism in the sole of the foot that increases venous outflow and reduces stasis in immobilized patients while electrical stimulation involves the induction of contractions that are designed to increase venous blood flow velocity out of the legs (12). NICE guidelines emphasize on the need to measure the legs and use the correct size of stockings which should not be used among patients with suspected or proven arterial disease, peripheral arterial bypass grafting or neuropathy, in patients with fragile skin, dermatitis, gangrene or recent skin graft (10). Major hindrances related to successful use of the IPCD's include poor compliance, lack of reliable battery power sources for the devices and cost as well as their availability.

Table 2

Recommendations for prevention of VTE in THR and TKR by ACCP, NICE and SA guidelines

Guideline	Mechanical methods recommended	Pharmacological thromboprophylaxis agents recommended	Timing of pharmacological prophylaxis	Duration of pharmacological prophylaxis	Use of inferior vena Cava filters
ACCP	Portable battery powered IPCD	LMWH, Fondaparinux, Apixaban, Dabigatran, Rivaroxaban, LDUH, Vitamin K Antagonists, Aspirin	LMWH-12 or more hrs preoperatively/ 12hrs or more postoperatively	THR- 35 days TKR- 10 to 14 days	Not recommended
NICE	GCS, IPCD & Foot impulse devices	Dabigatran, Fondaparinux, LMWH, Rivaroxaban	Dabigatran- 1 to 4 hrs after surgery Fondaparinux - 6 hrs postoperatively LMWH (or UFH) - 6 to 12hrs postoperatively Rivaroxaban - 6 to 12 hrs postoperatively	THR- 28 to 35 days TKR- 10 to 14 days	Recommended in high risk cases where mechanical or pharmacological prophylaxis is contraindicated
S. African Society of H & T	IPCD	LMWH (Dalteparin or Enoxaparin),Dabigatran, Rivaroxaban, Fondaparinux	LMWH within 6-12 hrs postoperatively Fondaparinux: 6-8hrs postoperatively Dabigatran -4hrs & Rivaroxaban -6hrs postoperatively	THR- 5 Weeks TKR- 2 Weeks	Not mentioned

Pharmacological thromboprophylaxis: The NICE, ACCP and South African guidelines recommend that thromboprophylaxis should be offered to patients undergoing TKR and THR in cases where the risk of VTE outweighs the bleeding risk. The three guidelines concur on and recommend the use of the following pharmacological agents in the prevention of VTE: Low Molecular Weight Heparin (LMWH), Fondaparinux, Dabigatran and Rivaroxiban. Additionally the ACCP further recommends the use of Apixaban, Low Dose Unfractionated Heparin (LDUH), Adjusted Dose Vitamin K antagonist (VKA) and Aspirin. The NICE guidelines further recommend the use of Unfractionated Heparin (UFH). Table 2 summarizes the key recommendations by these guidelines regarding the use of mechanical and pharmacological prophylaxis of VTE in patients undergoing major orthopaedic surgery including TKR and THR (9-11).

Thromboprophylaxis with Novel Oral Anticoagulant (NOAC) agents: Three NOAC agents Apixaban, Rivaroxaban and Dabigatran have been recently launched and are available in many countries worldwide following their demonstration of several advantages over traditional anticoagulants in the DVT prevention indication including simple oral fixed doses without any need for routine coagulation monitoring (13). All the three guidelines under this review recommend the use of the NOAC agents for the prevention of VTE after elective hip and knee replacement surgery. These recommendations are based on Randomised Clinical

Trial (RCT) data that has been published where the three agents demonstrated acceptable efficacy and safety profiles in comparison to enoxaparin. Most recently Apixaban, a factor Xa inhibitor has been introduced in the United States of America (USA) where other NOAC agents Rivaroxaban and Dabigatran were launched earlier. The ADVANCE 1 to 3 studies evaluated and established Apixaban's efficacy and safety in preventing DVT amongst patients undergoing THR (ADVANCE 1 & 2) and TKR (ADVANCE 3) when compared to Enoxaparin (14-16). Rivaroxaban is another factor Xa inhibitor that demonstrated efficacy and safety in preventing DVT post hip and knee replacement surgery in the RECORD 1 & 2 (THR) and RECORD 3 & 4 (TKR) studies where it was compared to Enoxaparin (17-20). Dabigatran, a direct thrombin inhibitor was compared to Enoxaparin where the efficacy and safety of Dabigatran in preventing DVT was evaluated and established for the TKR indication in the REMODEL and REMOBILIZE (21,22) studies and for the THR indication in the RENOVATE and RENOVATE 11 studies (23,24). Despite the publication of these RCT data the long term post-marketing safety of the NOAC agents is yet to be established. Furthermore to date no antidotes have been developed for any of these NOAC agents.

The guidelines in this review recommend dosage, initiation and discontinuation of the NOAC therapy based on the above trials data in line with the recommendations of the individual drug manufacturers. Where the facilities permit the NOAC agent activity

may be measured using anti-Xa assay which uses rivaroxaban specific calibrator (for rivaroxaban) and diluted thrombin time or ecarin clotting time for dabigatran. The SA guidelines recognize that routine coagulation assays may be affected by the NOAC's with dabigatran prolonging the partial thromboplastin time and rivaroxaban affecting the International Normalized Ratio (INR). Although the NOAC do not have specific antidotes their durations of action are relatively short (1.5-3hrs) when renal function is optimum. It is therefore paramount to check the renal function status of the patients and take it into consideration along with their ages when recommending the use of these agents. Various measures to manage bleeding episodes from the NOAC agents include stopping the drugs, application of local compressions, surgery to achieve haemostasis and supportive measures such as fluid therapy, haemodynamic support and transfusion of blood and blood products (11).

The NOAC agents dabigatran and rivaroxaban are currently registered and available for DVT prophylaxis treatment in Kenya. The use of these agents is on the rise particularly in the private hospital setup where the drugs are available although agents that have traditionally been used in the past such as LMWH, warfarin and aspirin are still being widely prescribed. The limited use of the NOAC agents to the private sector may partly be influenced by the direct cost implications of purchasing the medications which are relatively higher priced in comparison to older molecules such as warfarin and aspirin. A comparison of the daily cost of treatment with the NOAC agents versus originator alternative molecules was obtained from several Nairobi hospitals and their averages are outlined in Table 3. However readers are advised to check the actual prices in their institutions since we established there are price variations from one hospital to another. Furthermore they should also countercheck for availability and costing of competitive generic anticoagulants in hospitals where they are stocked. Clinician's choices of prophylaxis methods could presently be influenced by the available treatment options, the patient's physical and economic status and may further be affected by the hospital and health insurance policies. While selecting chemoprophylaxis further consideration needs to be given to the safety of the agents chosen, the inconvenience that may be experienced such as when monitoring coagulation profiles in the case of warfarin which can prolong the hospitalization period and the patient compliance that may be reduced when the patients have to inject themselves with anticoagulants after discharge from hospital. Nevertheless a clearer understanding of the country's priorities with regard to future policy on the use of various thromboprophylactic methods can best be reached after a pharmaco-economic cost-benefit analysis has been conducted.

Table 3

Daily cost of treatment with originator anticoagulant agents in Kenya

Anticoagulant agent	Average cost of daily treatment in Kenya shillings	Daily cost of treatment in United States Dollars
Warfarin 5mg, 3mg, 1mg	7	0.08
Aspirin 75mg, 100mg	5	0.06
Dabigatran (2x110mg or 2 x75mg)	306	3.56
Rivaroxaban 10mg	315	3.67
LMWH (40mg vial)	808	9.4
Fondaparinux 2.5mg	360	4.2

Thromboprophylaxis with aspirin: Randomised controlled trials, meta-analyses and other large pooled retrospective reviews have failed to consistently arrive at the same conclusions regarding the efficacy and safety of aspirin as an option for VTE prophylaxis in patients undergoing TKR, THR and HFS (25). Aspirin is widely available, cheap and easy to administer orally for prevention of VTE in surgical patients. However unlike the ACCP, both NICE and AAOS recommend the discontinuation of antiplatelet agents (such as aspirin and clopidegrol) before patients undergo hip and knee surgery owing to the likelihood of increased perioperative blood loss (9, 10). The ACCP's recommendation for the use of aspirin is based on the review of moderate quality evidence which concluded that low-dose aspirin when given before major orthopaedic surgery and continued for 35 days will result in seven fewer symptomatic VTE's per 1,000 at the expense of a possible three more major bleeding episodes and two more nonfatal myocardial infarctions per 1,000 resulting in a close balance between desirable and non-desirable effects (9). The largest RCT enrolled 13,356 patients and evaluated the efficacy of aspirin versus placebo in preventing VTE in patients undergoing elective hip or knee arthoplasty or fracture neck of femur surgery. Patients were randomized to receive 160mg of aspirin or placebo for 5 weeks. There was a statistically significant difference between aspirin and placebo among patients who developed a fatal PE in favor of aspirin but no difference in non-fatal PE (26). In the Pulmonary Embolism Prevention (PEP) trial aspirin significantly reduced the risk of any DVT by 29%, any PE by 43% and fatal PE by 58% (25). A meta-analysis of aspirin trials in 26,890 high-risk medical, general surgical and orthopaedic patients showed that aspirin compared with control (placebo or no treatment) reduced the risk of DVT by 37% and PE by 53% (27). The lack of standardization of bleeding

definitions has made the comparison of aspirin bleeding data to other agents difficult. Large meta-analyses and other pooled analyses with tens of thousands of patients that compared aspirin to LMWH and warfarin reported no significant differences in major bleeding indices, increased rates of major bleeding with LMWH and warfarin and increased operative site bleeding with LMWH and warfarin (25). The SA guidelines acknowledge that aspirin offers weak VTE prophylaxis when compared with other agents that are used for prophylaxis such as LMWH without expressly recommending its usage (11). Stewart *et al* (25) while comparing the AAOS and ACCP guidelines conducted a literature search that reviewed all the publications including RCT's and meta-analyses that evaluated the use of aspirin in prevention of VTE among orthopaedic surgery patients since 1986. They concluded that the studies have failed to consistently show a benefit in the reduction of VTE after TKA, THR and HFS in patients receiving aspirin. They further concluded that current Surgical Care Improvement Project (SCIP) measures do not include aspirin as an appropriate sole option for preventing VTE but in patients undergoing elective TKR or who have a contraindication to pharmacologic prophylaxis and undergo a THR or HFS, aspirin in conjunction with compression devices as part of a multimodal approach would meet these measures (25).

Thromboprophylaxis with Vitamin K antagonists (Warfarin): Among the three guidelines under consideration only the ACCP recommends the use of adjusted dose Vitamin K antagonists (VKA) for thromboprophylaxis after TKR and THR surgery. The ACCP recommendation for the use of warfarin is based on the consideration of several RCT's in TKR and THR where LMWH was compared to warfarin in more than 9,000 patients for initial prophylaxis. The results of these trials failed to prove or refute a difference in PE rates but LMWH use was associated with significantly less asymptomatic DVT at the cost of an increase in major bleeding events (9). Based on the RCT's that they considered the ACCP estimates that there will be three fewer symptomatic VTE events per 1,000 with the use of LMWH compared to warfarin a benefit that is closely matched with an increase of four major bleeding events per 1,000. Parvizi *et al* (28) performed a retrospective, single-center database search and identified over 28,000 patients who underwent Total Joint Replacement (TJR) surgery between January 2000 and June 2012. The patients involved in this data search had been treated for VTE prophylaxis with aspirin or warfarin aiming for an International Normalized Ratio (INR) of 1.5 to 1.8. The researchers obtained data on the incidence of PE, DVT, haematoma formation and other complications for 90 days after surgery. After analysis of the data they concluded that TJA patients treated with aspirin had a lower rate of PE

and DVT, fewer wound related problems and a shorter hospital stay than those treated with warfarin. Johnson *et al* (29) reviewed several RCT's and meta-analyses of trials that evaluated the safety and efficacy of VKA versus other forms of thromboprophylaxis including placebo, dextran, antiplatelet agents, mechanical thromboprophylaxis, LDUH and LMWH in orthopaedic surgery patients. Compared to placebo (no treatment) VKA yielded a Relative Risk Reduction (RRR) of 56% for DVT and 23% for PE but with a significantly higher rate of wound haematoma. However when compared to LMWH VKA was associated with higher rates of total and proximal DVT without significant differences in the rates of major haemorrhage or wound haematoma. In conclusion they observed that warfarin is significantly less effective than LMWH for preventing DVT's (29).

Warfarin is a coumarin derivative that interferes with the production of clotting factors. There is a time lag of many hours between the dosing time and the response which necessitates the monitoring of warfarin until stable anticoagulation is achieved (30). Warfarin can be difficult to dose properly because it can interact with food and drugs and can be affected by the patient's genetic predisposition. It also has a narrow therapeutic index which when coupled with its hepatic metabolism makes the onset, duration and offset of action unpredictable (28). The use of warfarin for thromboprophylaxis of lower limb surgery has been associated with a delay in discharge from hospital to stabilize the INR (30). This results in extra costs and unnecessary use of resources such as bed space and nursing time leading to an additional cost of 417 sterling pounds purely in terms of bed occupancy (30). Further caution needs to be exercised when recommending warfarin to patients with Human Immunodeficiency virus (HIV) and particularly the ones who are receiving antiretroviral (ARV) medications. Warfarin undergoes liver metabolism by Cytochrome P2C9 which is an isoenzyme of cytochrome P450 whose activity could be affected by ARV's. Nevirapine has been shown to decrease warfarin concentration probably through CYP2C9 induction (31). Bonora *et al* (31) reviewed several case reports and observed clinically significant drug interactions when efavirenz or lopinavir-ritonavir were co-administered with warfarin suggesting the need for careful clinical monitoring and warfarin dose adjustments. Sequinavir, indinavir, nevirapine, nelfinavir and ritonavir may necessitate an increase in the dosage of warfarin (32).

Thromboprophylaxis with parenteral anticoagulants: Parenteral anticoagulant therapy using LMWH, LDUH and fondaparinux is recommended by all the three guidelines under this review. For TKR and THR surgery LMWH consistently reduces asymptomatic DVT by close to 50% and has become the thromboprophylactic agent against which newer drugs are compared

(9). Several studies have been published which demonstrated the efficacy and safety of LMWH in decreasing the incidence of VTE after arthroplasty (33-36). The ACCP recommends that prophylactic therapy with LMWH should be initiated 12 hours before or after surgery while the South African and NICE guidelines recommend it to be started between 6 -12 hours postoperatively. The patient's platelet count should be checked on initiation of LMWH, after 5 days and regularly thereafter while on therapy (11). Anticoagulant activity for patients on treatment with LMWH can be measured using an anti-Xa activity assay which should be calibrated for each LMWH tested. Target levels for anti-Xa activity during prophylaxis treatment should be 0.3 to 0.5 anti-Xa units/ml of blood. The use of LMWH and any other haemostatically active agents should be discontinued if there is severe bleeding in which case the administration of protamine sulphate at a dose of 1 mg should be considered (11). Based on moderate quality evidence the ACCP guidelines recognizes that fondaparinux reduces 12 symptomatic VTE's per 1,000 a benefit that would be offset by an increase of at least 12 major bleeds per 1,000 . The guideline further estimates a baseline risk reduction of 13 symptomatic VTE's per 1,000 with UFH with an increase in major bleeding events of 4 per 1,000 with little or no effect on overall mortality (9).

Choice of anaethesia: When NOAC agents are used for thromboprophylaxis in orthopaedic surgery the performance of neuraxial anaesthesia is a safe method if it is based on the pharmacology of drugs(37). The NICE guidelines recommend the use of regional anaesthesia since it carries a lower risk of VTE compared to general anaesthesia. They further advice against the routine offering of pharmacological or mechanical VTE prophylaxis to patients having surgery with local anaesthesia infiltration with no limitation of activity (10). South African guidelines recommend neurological monitoring for a minimum of 12 hrs after neuroaxial blockade in association with anticoagulation. Further recommendations depend on the choice of anticoagulant (11). The catheter should not be placed or removed within 12hrs of a dose of LMWH, LMWH should not be commenced less than 2hrs after insertion or removal of a neuroaxial catheter and LMWH should be delayed for at least 24hrs if there is blood in the needle of a neuroaxial catheter during needle insertion. Regarding neuroaxial blockade in conjunction with the NOAC epidural catheter removal should take place 22 to 26hrs after the last dose of a NOAC. Following removal of the catheter NOAC should not be administered earlier than 1hr (Dabigatran) and 6 hrs (Rivaroxaban).

CONCLUSIONS

Significant reduction in the incidences of VTE post hip and knee replacement surgery can be achieved through the use of various mechanical and pharmacological methods some of which are available locally and worldwide. There is no VTE prevention consensus statement or guidelines in Kenya despite the gradual increase in the number of patients who are undergoing hip and knee replacement surgery and those who are receiving thromboprophylaxis treatment. The choice of an appropriate VTE prophylaxis measure may be influenced by the patient's VTE and bleeding risk profiles as well as the available prophylactic options with the cost of treatment and drug side effects and interactions in mind. This is probably the appropriate time for Kenya to develop and benchmark VTE prevention guidelines against the standard international practice.

REFERENCES

1   Virchow, R. Never fall von todlichen, Emboli der lungenarterie. *Arch Pathol Anat*. 1856; **10:** 225-228.

2   EMedicine (2013): DVT; http;//emedicine. medscape. com/article/191303

3   Geerts, W.H., Heit, J.A., Clagget, G.P., *et al*. Prevention of venous thromboembolism. *Chest.* 2001; **119**: 132S-175S.

4   Goldhaber, S.Z, Hennekens, C.H., Evans, D.A. *et al*. Factors associated with correct antemorterm diagnosis of major pulmonary embolism. *Am J Med*. 1982; **73**: 822-826.

5   Nutescu, E. Assessing, preventing and treating venous thromboembolism: Evidence based approaches. *Am J Health-Syst Pharm*. 2007; **64** (7): S5-S13.

6   Sullivan, D.S., Kahn, S.R., Davidson, B.L., *et al.* Measuring the outcomes and pharmacoeconomic consequences of venous thromboembolism prophylaxis in major surgery. *Pharmacoeconomics*. 2003; **21**(7): 477-496.

7   White, R.H., Romano, P.S., Zhou, H., *et al.* Incidence and time course of thromboembolic outcomes following total hip or knee arthoplasty. *Arch Intern Med*. 1998; **158**: 1525-1531.

8   AAOS, Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthoplasty. Evidence based guideline & evidence report 2011 AAAhttp://www.aaos.org/research/guidelines/guide.aspU

9   Falck-Ytter, Y., Francis, C.W., Johnson, N.A., *et al*, American College of Chest Physicians Evidence based clinical practice guidelines; Prevention of VTE in orthopaedic surgery patients; Antithrombotic therapy and prevention of thrombosis, 9th ed, Chest 2012; 141; e278s-e325S DOI 10, 1378/chest. 11-2404.

10   National Institute for Health and Clinical Excellence; Venous Thromboembolism: Reducing the risk, NICE Clinical guideline 92 Jan 2010; www.nice.org.uk

11   Jacobson, B.F., Louw, S., Buller, H., *et al*. On behalf of the South African Society for Thrombosis and Haemostasis; Venous thromboembolism-prophylactic and therapeutic guidelines. *S. Afr Med J.* 2013; **103: No 4(Part 2).**

12   Machin, S.J. Prevention of Thromboembolism in Orthopaedic Surgery, Expert Lecture in Thromboprophylaxis, www.evolving-medicine. com 2009

13   Perez, A., Eraso, L.H. and Merli, J. Implications of new anticoagulants in primary practice. *Int J Clin Pract*. 2013; **67**(2): 139-156.

14   Lassen, M.R., Raskob, G.E., Gallus, A. *et al*. Apixaban or Enoxaparin for thromboprophylaxis after knee replacement. *N Eng J Med*. 2009; **361**: 594-604.

15   Lassen, M.R., Raskob, G.E., Gallus, A. *et al*. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): A randomized double blind trial. *Lancet*. 2010; **375**: 807-815.

16   Lassen, M.R., Gallus, A., Raskob, G.E., *et al*. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Eng J Med.* 2010; **363**: 2487-2498.

17   Eriksson, B.I., Borris, L.C., Friedman, R.J. *et al*. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthoplasty. *N Eng J Med.* 2008; **358**: 2765-2775.

18   Kakkar, K.A., Brenner, B., Dahl, O.E. *et al.* Extended duration rivaroxaban versus short term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double blind , randomized controlled trial. *Lancet*. 2008; **372**:31-39.

19   Lassen, M.R., Ageno, W., Borris, L.C. *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Eng J Med.* 2008; **358**: 2776-2786.

20   Turpie, A.G.G., Lassen, M.R., Davidson, B.L. *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD 4): a randomized trial. *Lancet.* 2009; **373**: 1673-1680.

21   Eriksson, B.I., Dahl, O.E., Rosencher, N. *et al*. Oral dabigatran etexilate versus subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement surgery; the REMODEL randomized trial. *J Thromb Haemost.* 2007; **5**: 2178-2185.

22   The RE-MOBILIZE writing committee. Oral thrombin inhibitor dabigatran etexillate versus North American exoxaparin regimen for prevention of venous thromboembolism after knee replacement surgery. *J Arthroplasty*. 2009; **24**; 1-9.

23   Eriksson, B.I., Dahl, O.E., Rosencher, N. *et al*. Oral dabigatran etexillate versus enoxaparin for prevention of venous thromboembolism after total hip replacement; a randomized double blind non-inferiority trial. *Lancet.* 2007; **370**: 949-956.

24   Eriksson, B.I., Dahl, O.E., Huo, M.H., *et al.* Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip athroplasty (RE-NOVATE 11). A randomized, double blind, non-inferiority trial. *Thromb Haemost.* 2011; **105**: 721-729.

25   Stewart, D.W. and Freshour, J.E. Aspirin for the prophylaxis of venous thromboembolic events in orthopedic surgery patients; A comparison of the AAOS and ACCP guidelines with a review of the evidence. *Annals Pharmacotherapy.* 2013; **47**(1): 63-74.

26   Leclerc, J.R., Geerts, W.H., Desjardins, L. *et al*. Prevention of deep vein thrombosis after major knee surgery- a randomized double blind trial comparing a low-molecular weight heparin fragment (enoxaparin) to placebo. *Thromb Haemost.* 1992; **67**(4): 417-423.

27   Eikelboom, J.W., Karthikeyan, G., Fagel, N. *et al*. American Association of Orthopaedic Surgeons and American College of Chest Physicians Guidelines for venous thromboembolism prevention in hip and knee arthroplasty differ: What are the implications for clinicians and patients. *Chest.* 2009; **135**: 513-520.

28   Parvizi, J., Ibrahim, J.R., Tischler, E.H. *et al*. (2013); Aspirin vs Warfarin: Which is better at preventing VTE; http://www.aaos.org/news/aaosow/jun13/clinical1.asp

29   Johnson, J.L. and Riley, T.T. Oral options for VTE prophylaxis after orthopaedic surgery. *US Pharm.* 2012; **37**(2): HS-8-HS-11.

30   Dunbar, M.R., Upadhyay, P.K. and Karthikeyan, S. The use of warfarin as thromboprophylaxis for lower limb arthroplasty. *Annals Royal College of Surg Engl.* 2008; **90**: 500-503.

31   Bonora, S., Lanzafame, M., D'Avolio, A. Drug interactions between warfarin and efavirenz or Lopinavir-Ritonavir in clinical treatment. *Clinical Int. Dis*. 2008; **46**(1) 146 - 147.

32 AIDS Reader (2008): Challenge of coadministering antiretroviral therapy and oral antcoagulants in HIV-positive patients; http://www.theaidsreader.com/print/196530

33 Fuji, T., Ochi, T., Niwa, S. *et al*. Prevention of post-operative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty; two randomized , double-blind placebo controlled studies with three dosage regimens of enoxaparin. *J Orth Sci.* 2008; **13** (5): 442-451.

34 Samama, C.M., Clergue, F., Barre, J. *et al*. Arar study group, low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery. *Br J Anaesth.* 1997; **78**(6): 660-665.

35 Levine, M.N., Gent, M., Hirsh, J. *et al*. Ardeparin (Low-Molecular Weight Heparin) vs graduated compression stockings for the prevention of venous thromboembolism. A randomized trial in patients undergoing knee surgery. *Arch Int Med.* 1996; **156** (8): 851-856.

36 Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin; Pulmonary Embolism Prevention (PEP) Trial. *Lancet*. 2000; **355**: 1295-1302.

37 Tripkovi, B. and Sakic, S. New anticoagulants and regional anesthesia in patients undergoing orthopaedic surgery. *Periodicum Biologorum* 2011; **113** (2): 269-273.