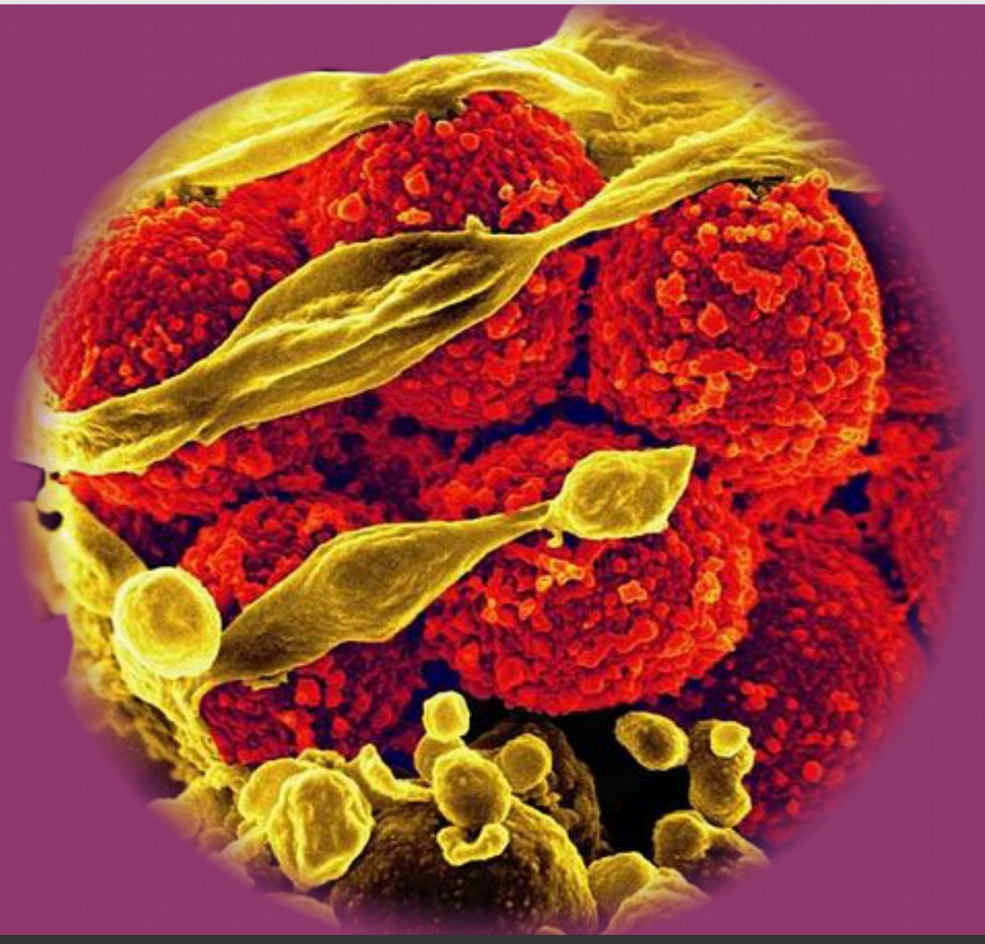
N S H B T

NIGERIAN JOURNAL OF HAEMATOLOGY

Journal of the Nigerian Society for Haematology & Blood Transfusion



ISSN: 2635-3024 **VOL. 2 NO. 1, MARCH 2019**

Special Feature:
Guidelines for the Management of Venous Thromboembolism in Nigeria.

Guidelines for the Management of Venous Thromboembolism In Nigeria

Nigerian Society for Haematology and Blood Transfusion

Preamble

The field of medicine has become so wide and the care and management of different conditions is transcending basic knowledge and requires guidelines for diagnosis, and prevention of several disease entities. Levels of medical practice differ from community to community and from one country to another. This is largely due to the fact that advancement in medical knowledge particularly diagnostic advancement and affordability of novel therapeutic interventions vary widely.

The subject of thrombosis has not received sufficient attention in medical practice in Nigeria. There are very few Haematologists in Nigeria today with special interest or sub- specialization in haemostasis (haemorrhagic and thrombotic disorders), thus few research efforts have been recorded in this subject area. Review of project dissertations to the National Postgraduate Medical College of Nigeria (NPMCN) amongst fellow pathologists show that very few theses are submitted related to the subject of haemostasis. Whereas, in many countries including some African countries, the epidemiology of thrombosis and thrombotic disorders (including the burden of the diseases, the common acquired predisposing factors as well as inheritable predisposing factors) have been well documented, no such data (particularly- country-wide based) is available for Nigeria. The available literature from Nigeria is scanty and fragmented.

We have no clear idea of the burden of thrombotic disorders in Nigeria, although we know from medical practice that several deaths post-surgery are related to thrombotic disorders. A number of cases of sudden deaths are diagnosed at post-mortem as being due to complication of thrombotic disorders. It is estimated from few hospital-based studies in Nigeria that inheritable predisposing factors to thrombosis may not be that rare. Factor V Leiden has been documented in at least 2% of normal blood donors in Nigeria1, other studies have shown that Protein C, Protein S, Plasminogen Activator Inhibitor levels deficiency may not be rare in Nigeria[2,3].

As part of its responsibility to Nigerians, the NSHBT is in a position to provide guidelines for prevention, diagnosis, care and treatment of diseases related to Haematology and Immunohaematological practice in Nigeria. With the support of few pharmaceutical companies in Nigeria, the Society has been able to produce Lymphoma Treatment Guidelines in Nigeria; this has undergone a few updates in the recent past[1].

At the Society's 42nd annual scientific and general meeting held in October 2016 in Lagos, the subject of thrombotic disorders in Nigeria came to fore and the Society received guests from the International Society on Thrombosis and Haemostasis (ISTH). During the conference, different aspects of thrombotic disorders were discussed, limitations in the country were identified with respect to diagnostic capacity, monitoring of anticoagulant therapy and affordability of newly available therapeutic intervention to Nigerians who suffer from thromboembolic disorders. At this conference ISTH charged and challenged Nigerian Haematologists to set up a Committee that should be saddled with the responsibility of:

1. Promoting research on thrombosis and bleeding disorders
2. Promoting increased level of exposure and training of its members in thrombotic and bleeding disorders and
3. Producing treatment guidelines for use by practitioners in Nigeria for thromboembolic disorders.

We thank the ISTH for its attendance at our meeting in the persons of Prof. Andreas Greinacher from Germany, Prof. Suikish Nair from India, Dr. Edoghogho Olayemi from Ghana and Dr. Claire Mclintock from New Zealand. We also appreciate some senior Haematologists in Nigeria who have shown interest in thrombosis and Haemostasis. In particular Prof. Etim Essien a retired Professor of Haematology and blood transfusion, Prof. Wuraola Shokunbi of University College Hospital Ibadan and the energetic Prof. Omolade Awodu of the University of Benin who is the Chairman of this guideline writing Committee and the eye of Nigeria at International fora in thrombosis and haemostatic disorders. This is the first effort in developing a guideline for the prevention, diagnosis, care, treatment and prophylaxis for thromboembolic disorders in Nigeria.

This guidance is written according to the current best practices as published. However every patient should be evaluated as a person and therapy should be individualized

THIS GUIDELINE IS REVIEWED BY EXPERTS IN THROMBOSIS AND BLEEDING DISORDERS OF THE EDUCATION SUBCOMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

INTRODUCTION

This guideline was drafted by a group of experts who are members of the Nigerian Society of Haematology and Blood Transfusion (NSHBT), all the authors are Consultant Haematologists who have trained and work in Nigeria and outside Nigeria. A search of literature was conducted, and the search covered articles published up until 2017.

Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of morbidity and mortality in hospitalized patients. For a long time, it has been regarded as a disease of the Caucasian, however over the last decade, with increasing interest, there is evidence that VTE is equally prevalent in blacks if not more than in the Caucasian populations[4]. Studies in predominantly black populations in the UK have shown that younger blacks present with VTE than whites and they have more proximal events compared to whites[5,6].

Venous thromboembolic disorder refers to clotting disorder that remain undiagnosed in more than 50% of cases but may present precipitously with complications that may be life threatening such as massive pulmonary thromboembolism and occasionally the phenomenon called phlegmasia cerula dolens which refers to massive swelling of the whole of the limb with attendant pulling of blood to the limb leading to hypovolemic shock and death. Evidence now abounds that the disease is more prevalent in the blacks than in the whites. In a review by Tyler *et al* of venous thrombosis in blacks[4], data were presented to show that;

a. The overall incidence of VTE is 30% to 60% higher in blacks than in whites. This holds true across age groups and for both men and women.
b. The overall incidence of PE is higher for blacks, as is the proportion of VTE patients who have a PE.
c. Pregnancy-associated VTE rates are also higher in blacks than in other groups.

Local evidence also suggests that several deaths occur among Nigerians due to complications of VTE that were not diagnosed ante-mortem. In a review of records of autopsy performed at the University College Hospital (UCH) Ibadan between 1991 and

1998, Sotunmbi *et al* reported 29 deaths (2.9%) of 989 records to be due to fatal pulmonary embolism. Of these 29 patients, 37.7% were VTE attributable to malignancy, 27.6% attributable to prolonged immobility of more than 4 days duration. Another 24%

And 20% were ascribed to neuromuscular paralysis and sepsis respectively. Other documented predisposing factors were multiple trauma involving the pelvis 17.2%, major surgery – 13.8%, Congestive Cardiac Failure (CCF) 3.4% and obesity also 3.4%[7].

In another publication from UCH, Okunade et al, presented a five-year report (1986 -1990) of patients with VTE seen at the haematology outpatient's clinic of the hospital. A total of 60 diagnoses of VTE were made. Ten of these were diagnosed to have PE and the rest were DVT, 80% of which had proximal thrombosis (iliofemoral thrombi). Unlike the autopsy report from the same hospital, females were more affected in a ratio of 2:1 and recent surgery was the commonest predisposing factor. A few of the patients (5%) had no identifiable risk factors[8].

It appears the incidence of VTE is largely dependent on available diagnostic capacity. Whereas in the 5-year period between 1986 and 1990 only 60 patients were reported at the haematology outpatient clinic of UCH, in 2007 – 2012 however, the number of diagnosed cases of VTE was 178[9]. The available diagnostic methods in the earlier years were traditional venogram and presence of classic VTE symptoms. In the later years, symptoms are better recognized probably because of a heightened clinical suspicion as well as availability of prediction models. The advent of sensitive, non-invasive radio- imaging technique has made identification of less massive thrombotic disorder a lot easier and precise. Thus, in the late report from a cohort of UCH patients (178), 76% of diagnoses were distal thrombosis; 3% had pulmonary embolism, the male to female ratio also changed as more males are now detected as having VTE even though there is still overall female preponderance in a ratio of 1:1.2. Unlike in the earlier report, CVA with possible prolonged immobility as well as malignancies (in particular prostate carcinoma) were the most common predisposing factor in 14.5% and 12.2 % respectively.

In addition to the earlier report, HIV/AIDS was also identified as a predisposing factor in

6.7% of the patients. The distinguishing feature of HIV-associated VTE is a long cord of thrombus. The mechanism by which HIV/AIDS predisposes to thrombosis has been put forward by the researchers from the Lagos University Teaching Hospital. In the setting of HIV/AIDS, large concentrations of acute phase reactant proteins are elaborated. Among these proteins is the C4b binding protein, the level of which has been shown to be in multiples of the usual concentration in health. The C4b binding protein complexes with Protein S resulting in acquired depression of Protein S.[10]

In a small report involving 22 cases of diagnosed VTE from the north-eastern part of Nigeria between 1996 and 1999, obesity, abdominal and pelvic surgery, advancing age and puerperium were identified as the leading predisposing factors. In this report, proximal VTE was seen in 64% of the patients predominantly affecting the left limb[11].

The four reports so far reviewed from Nigeria showed no consistent predisposing factors to thrombosis. Whereas the autopsy report concluded that malignancies was the commonest associated predisposing factor, reports based on clinical and laboratory diagnosis showed that recent surgery and obesity were the commonest associated factor at one point in time and a later review of clinic experience showed that CVA and malignancies were the commonest risk factors.

In an African study designed to document the predisposing factors to VTE, both acquired and inherited predispositions were evaluated. This was a study conducted in several hospitals in Senegal involving 105 cases of VTE and 200 normal controls. In a logistic regression associating possible risk factors with DVT for Senegalese, age, obesity, sickle cell disease (SCD) and Protein C deficiency failed to show significant association with VTE in the logistic regression. However, gender, protein S deficiency, surgery, varicosity, non-O ABO blood group and presence of anti-phospholipid antibody were significantly associated with VTE. In this study, 16 of 105 cases and 2 of the controls had Protein S levels less than 48.4% in the functional assay suggesting that about 16% of cases of VTE among Africans may have Protein S deficiency as the underlying factor.[12]

Many of the studies on VTE predisposing factors highlighted above are not all inclusive. The wider literature as depicted in the table below showed that factors that could predispose to VTE can be categorized and such categorization can be used as basis of prophylactic interventions. Thus, individual categorized as having low risk to VTE is an individual of any age group who has none of the listed conditions associated with moderate, high or very high risks. It must be noted however, that this categorisation is not absolute and the development of VTE remains an interplay of risk factors.

Table 1: VTE Predisposing Factors by Category of Risks

Low Risk	Moderate Risk	High Risk	Very High Risk
Any age without known risks	Age >40yrs plus poor ambulation § Oral contraceptive pills/ estrogen § Chronic venous insufficiency § Pregnancy and puerperium (6 weeks) § Long haul flights (>8 hours) in the last month § Trauma/abdominal surgery § Acute inflammatory or infectious disease § Rheumatological disease	Respiratory failure/ decompensated § COPD/Pneumonia § Cardiac failure/COPD § Obesity § Inflammatory bowel disease § M yeloproliferative syndrome § Active cancer or § cancer therapy § Nephrotic syndrome § Extensive burns § M yocardial infarction/ acute coronary syndrome § Critical care patients § Sepsis § Stroke § Lower limb immobility	Major trauma § Thrombophilia § History of DVT/PE § Respiratory failure on mechanical support

Although it is easy to recognize most of the listed risk factors as they are predominantly clinical diagnosis, the risk factor listed as thrombophilia refers to inherited predisposition which requires laboratory investigation to diagnose. Among the inherited thrombophilic states, there are those that are said to be very common, those that are said to be rare and those that are very rare as shown in the table below.

Table 2: Inherited thrombophilic states

Common	Rare	Very Rare
§ Factor V Leiden § Prothrombin G20210A § Increased Factor VIII levels § Homozygous C677T § Polymorphism in methylene § tetrehydrofolate reductase	§ Protein C Deficiency § Protein S Deficiency § Antithrombin deficiency	§ Dysfibrinogenemia § Homozygous homocystinuria

Our belief is that by the next update of this first guideline, the epidemiology of VTE in Nigeria will have been better studied and understood including the acquired as well as the inherited thrombophilic states.

Pathophysiology of Venous Thromboembolism

The blood must remain in its fluid state for as long as it remains within the vascular tree. The blood must also be able to turn to clot whenever there is a cut or injury to the blood vessel such that the clot blocks the injured part and prevents the individual from haemorrhaging to death. The pathophysiological mechanisms which ensure that the blood remains in its fluid state with the vascular tree and that it turns to a clot when there is damage unto the blood vessel have been termed haemostasis. These haemostatic mechanisms are related to factors that are found within the blood vessel itself, (particularly within the sub-endothelial structures and the endothelial cells) the rate of flow of blood and the proteins in the plasma with

coagulant and anticoagulant effects. All these have been termed the Virchow's triad.

The major steps leading to formation and deposition of clot are depicted in Figures 1-4. As shown in Figure 1, the initial event towards clot formation is the expression of tissue factor (TF) on the cell membrane. The pathological stimuli whether physical trauma, endotoxinaemia from variety of infections, immune complex deposition, atheromatous plaques e.t.c. all cause cytoplasmic TF to become expressed on cell membrane particularly the endothelial cells. Such expression makes flowing Factor VII in the plasma attracted to it to form TF-FVII complex. FVII in the complex becomes activated. The resulting TF-FVIIa complex in the presence of Ca++ attracts FX from the flowing blood to the membrane such that TF-FVIIa complex now activates FX to FXa.

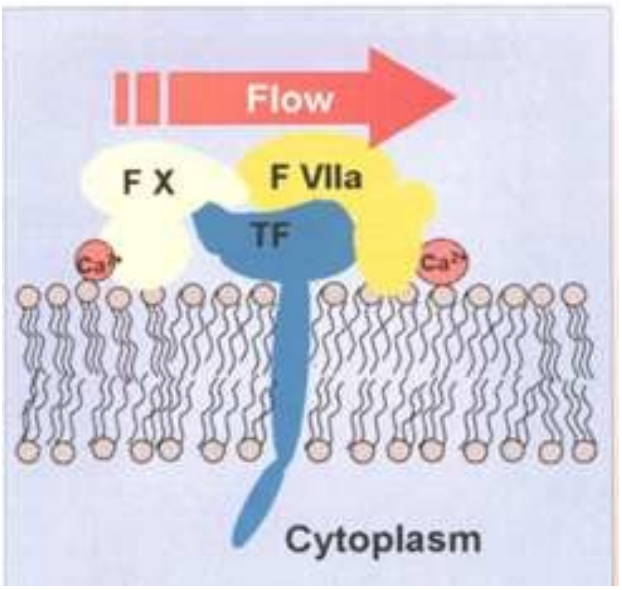


Figure 1: Cellular Express of Tissue Factor and the activation of Factor X

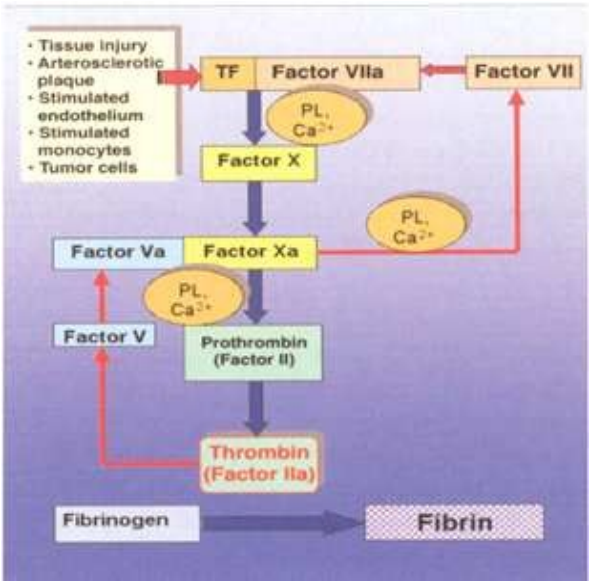


Figure 2: Generation of Limited amount of Thrombin from TF-FVII complex activation of FX

The limited amount of thrombin generated above is used to activate

a. FXI to FXIa which in turn activates FIX to FIXa
b. FVIII to FVIIIa and this complexes FIXa as a coenzyme to activate much more FX than was activated by TF-FVIIa complex
c. More FV to FVa

Figure 2 depicts how the membrane generated FXa recruits and activate FV to FVa. The Complex of FXa-FVa together with phospholipid and Ca++ has been termed tenase complex or prothrombinase. The complex converts prothrombin to limited amount of thrombin which is used primarily not to convert fibrinogen to fibrin but to serve in a feedback mechanism to generate more activated Factor X through factor IX activation as depicted Figure III.

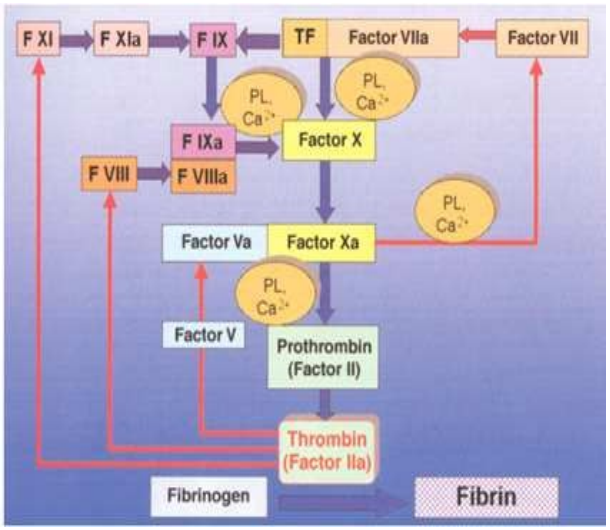


Figure 3: Propagation of thrombin generation

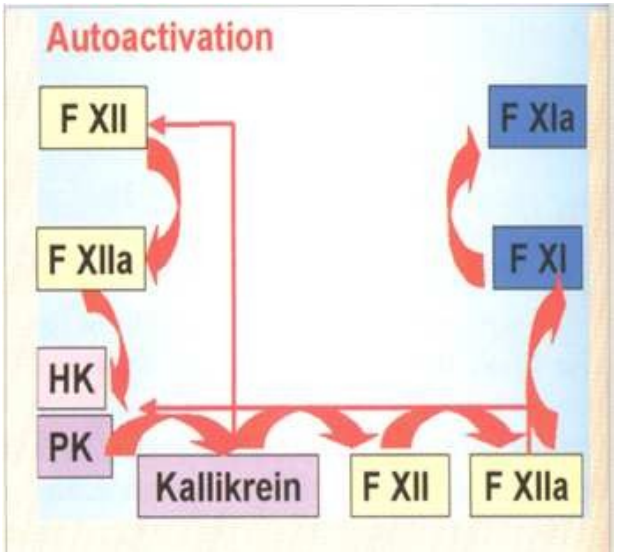


Figure 4: The Contact Activation Pathway.
KEY: HK-high mol weight kininogen, PK- pre-kallikrein

A little amount of thrombin may also be generated from the so called contact pathway which exists primarily to initiate lysis of excessively formed thrombus. The contact of sub-endothelial collagen with flowing Factor XII not only result in generation of urokinase type plasminogen activator (uPA) but also activation of FXI to generate thrombin (Figure 4).

The Kallikrein from this pathway also activates pro urokinase to urokinase or the so called urokinase type plasminogen activator not depicted in the Figure

Clinical Features for Venous Thromboembolism

Most of the clinical features of VTE are nonspecific[13, 14]. The clinical features depend on the location of the affected vessel and degree of occlusion. Both DVT and PE may be asymptomatic, and up to 50% of DVT patients have been reported to be asymptomatic. Therefore, a high index of clinical suspicion is required.

Deep Venous Thrombosis: In symptomatic DVT, the patient presentations are varied and they may include pain, swelling, warmth and discoloration of the affected limb or tissue. With careful examination, the physician would observe swelling which is usually unilateral. In the case of DVT of lower limb, one of the signs relate to a wider circumference of the affected limb (more than 3cm) when compared with the contralateral limb. This is measured at 10cm below the tibial tuberosity or 10-15cm above the upper edge of the patella. Homan's sign and Pratt's sign may be present. There may be collateral circulation. There is usually some tenderness on palpation and presence of a palpable cord. With massive iliofemoral thrombus, phlegmasia cerulean dolens (a condition characterized by severe swelling, cyanosis and bluish discolouration of the extremity) is present.

Pulmonary Embolism: Symptoms and signs of PE are generally nonspecific as well. The size of the clot and occlusion site determines the extent and severity of the clinical features. Patients could present with fast and labored breathing, fast heart rate, chest pain, apprehension, anxiety, cough with or without haemoptysis, fever, sweats, syncope and fatigue. In addition to the above, the physician may notice cyanosis, rales, hypotension, arrhythmia, accentuated pulmonary closure sound and gallop heart sound[14]. Clinical pre-test probability is an important step in the integrated diagnostic strategies that employ clinical probability, D-dimer, CT angiography, lung scanning, and objective testing for deep vein thrombosis[15].

Diagnosis of VTE

The diagnosis of DVT and PE has evolved over the years. A strategy using an algorithm has become a practicable, safe and cost-effective means of investigating patients with suspected VTE. This algorithm involves the following main components in a step-wise approach:

1. Clinical prediction rules
2. D-dimer testing
3. Imaging techniques

In patients with suspected VTE, detailed clinical history as well as bleeding history and the use of aspirin and other antiplatelets drugs should be obtained. Examination and supportive work up investigations e.g. full blood count, prothrombin time, activated partial thromboplastin time, serum electrolyte, urea and creatinine, liver function tests (LFTs), electrocardiogram (ECG), chest x-ray (CXR), clotting profile, etc. should be carried out as appropriate and relevant to the individual patient.

1. Clinical Prediction Rules

The first step in the diagnosis of VTE is to use the clinical prediction rules. Well's prediction score is the most widely used and validated score in the diagnosis of VTE. This is shown below in the Tables 3 & 4.

Table 3: Clinical Prediction Rules for DVT[16]

VARIABLE	POINTS
Active Cancer (ongoing treatment or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of lower extremities	1
Recently bedridden for ≥ 3 days or major surgery within 4 week	1
Localized tenderness along distribution of deep venous system	1
Swelling of entire leg	1
Calf swelling ≥ 3cm compared to asymptomatic contralateral one (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to symptomatic leg	1
Collateral superficial veins (non - varicose)	1
Past history of DVTA	1
alternative diagnosis at least as likely as DVT	-2

< 0 points = low probability (prevalence of DVT 3%)
0-2 points = intermediate probability (prevalence of DVT 17%)
2 points = high probability (prevalence of DVT 75%) Dichotomized scores:
< 2 point = DVT Unlikely
2 points = DVT Likely

Table 4: Wells Clinical Probability Scores for Pulmonary Embolism [16]
Wells Clinical Probability for Pulmonary Embolism

Risk factors, symptoms or signs	Points
Signs or symptoms of DVT	3
Alternative diagnosis is less likely than PE	3
Heart rate > 100 bpm	1.5
Immobilization/surgery in the previous 4 weeks	1.5
Prior history of DVT or PE	1.5
Haemoptysis	1
Active Cancer	1

Three category (three level) scheme: Low probability <2.0 point
Intermediate probability 2.0-6.0 points
High probability ≥ 6.0 points

Two category (two level) scheme:
PE unlikely: 0-4 points
PE likely: > 4 points

2). D-Dimer Testing

This is a degradation product of cross-linked fibrin blood clot that is typically elevated in patients with acute venous thromboembolism. However, there are a plethora of other non-thrombotic disorders in which D-dimer may be elevated. These include among others, recent surgery, trauma, pregnancy, haemorrhage, cancer, DIC, old age, infection, etc. In VTE D-dimer is highly sensitive but non-specific! The usefulness of D-dimer lies in its negative predictive value!

It is preferable to use ELISA test which is very sensitive, 97-100% for D-dimer. Other forms of D-dimer assays include Latex agglutination method, Whole Blood Assay (SimpliRed), Turbidimetric Assay, and Immunofiltration Assay. The addition of D-dimer testing to the diagnostic algorithm has the potential to make the diagnosis of VTE in outpatients more convenient and economical. In patients who have unlikely clinical probability scores and a negative D-dimer test (using age-adjusted cutoff values forpatients aged ≥ 50 years) the diagnosis of DVT can safely be excluded without further diagnostic testing or treatment[17].

3). Imaging Techniques

Deep Vein Thrombosis

Compression ultrasonography (CUS) is the diagnostic imaging technique of choice for suspected cases of DVT. Non-compressibility of a venous segment is the most sensitive and specific diagnostic finding for a first episode of DVT. The addition of Doppler Scan **(especially with color flow)** is useful in accurately identifying specific vessels and to clear doubts about compressibility of particular segment[18].

Pulmonary Embolism

The most widely used and evaluated imaging techniques in PE diagnosis are Computerized Tomographic Pulmonary Angiography (CTPA) and Ventilation- Perfusion (V/Q) lung scans. CTPA is currently the preferred diagnostic test for PE because of its higher sensitivity and simpler reporting system. Other less favored imaging techniques include conventional Contrast Pulmonary Angiography, Thoracic Ultrasound and Magnetic Resonance Angiography (MRA)[18].

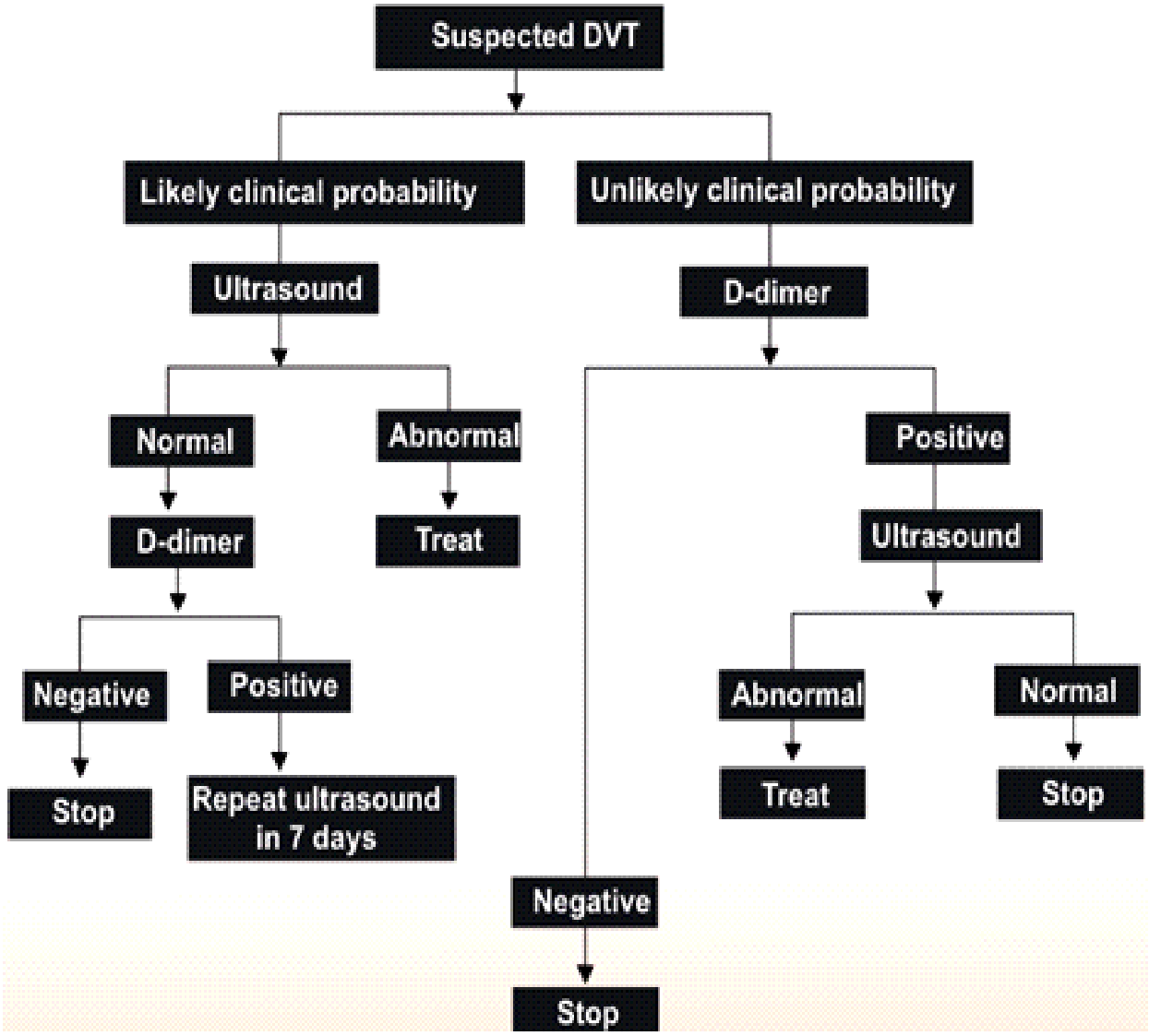


Figure 5: DVT Diagnostic Algorithm[16]

I. The first step is to use a validated clinical rule such as the Wells Score) to determine pretest probability
II. For UNLIKELY pretest probability a negative age-adjusted D-dimer test excludes DVT and negates the need for further diagnostic imaging.
III. All other patients may require imaging
IV. A negative D-dimer result should not be used to exclude VTE in patients with LIKELY clinical probability because of the higher false negative rate in this subgroup.

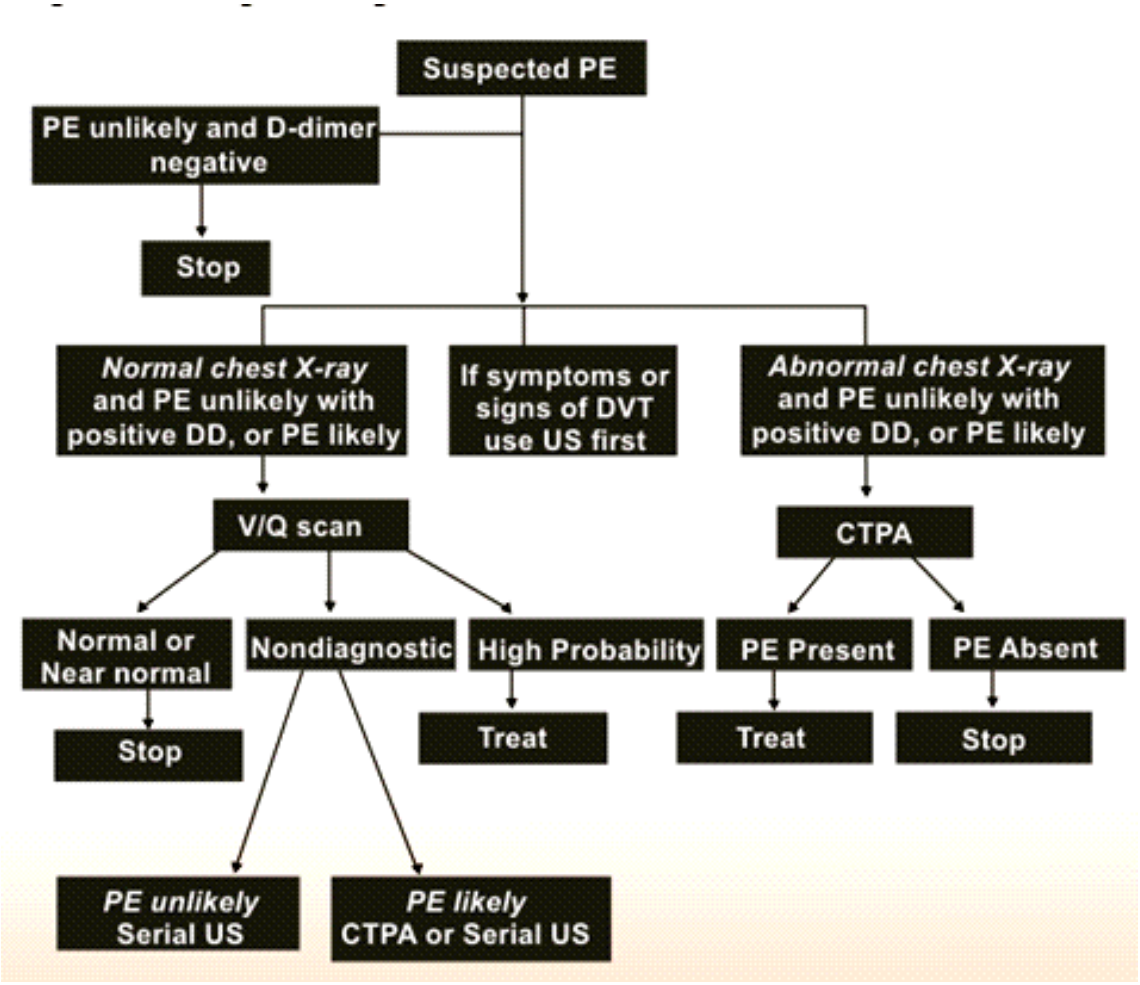


Figure 6: PE Diagnostic Algorithm[16]

a. Clinical assessment and D-dimer testing have the advantage of PE diagnosis in settings where radiographic imaging is not readily available
b. Thoracic Ultrasonography is positive in 20% of patients with clinical features of PE and in 50% of those with likely pretest probability and symptoms of DVT
c. The use of CTPA in combination with clinical pretest has a high negative and positive predictive value
d. Positive CTPA results can be considered diagnostic if the clinical pretest probability is high/likely or if the PE is located in a segmental or a larger vessel. If at the level of sub-segmental arteries, the result should be discussed with the radiologist to rule out false positive CTPA results[19].

Thrombophilia Testing

Inherited risk factors for venous thrombo-embolism have been identified progressively over the years. While testing for these risk factors is still controversial, the table below gives absolute risk information to help the clinician make decisions regarding testing and patient management[19]. Thrombophilic defects with annual risk of first VTE greater than 1% are classified as high risk and they are more frequently tested for. These include antithrombin deficiency, protein C and S deficiency. Patients who have the following features may be considered for thrombophilia testing:

§ Idiopathic (spontaneous) VTE in a patient < 50 years of age
§ Positive family history of VTE
§ Thrombosis in an unusual site
§ Recurrent VTE

Table 5: Thrombophilia: Grading the Risk[19]

Thrombophilic defect	Annual risk of first DVT	Relative risk (compared to community controls)	Risk of recurrence
Antithrombin deficiency Protein C deficiency Protein S deficiency	1.52 – 1.90%	15 – 19	At 5 yrs - 40% At 10 yrs – 55%
Factor V Leiden Prothrombin 20210A High FVIII	0.34 – 0.48%	3 – 5	At 5 yrs - 11% At 10 yrs – 25%
High FIX High FXI High TAFI Hyperhomocysteinemia	Not independent risk factors for venous Thrombosis Risk associated with high FVIII		

Key Diagnostic Recommendations

- § Patients should be assessed for clinical probabilities for DVT using Wells Score
- § Patients should be assessed for clinical probabilities for PE using Wells Score
- § Patients with likely probability of DVT should have Doppler Ultrasound scan (DUSS) and
  - If positive start treatment but
  - if negative D-dimer assay is required.
  - D-dimer should be done for all cases of suspected DVT where DUSS is not readily available
  - If D-dimer is negative DVT is excluded otherwise repeat scanning indicated in 1 week
- § Patients with unlikely probability of DVT should have D-dimer assay first
  - If negative DVT is excluded but
  - If Positive DUSS is indicated.
  - If DUSS is positive DVT is established otherwise it is excluded
- § Patients with likely probability of PE and have DVT diagnosed, PE is established
- § Patients with Unlikely probability of PE should have Chest X-ray, D-dimer and CTPA
  - If all are positive PE is established
  - If X-ray is positive, D-dimer is positive and CTPA is negative PE is excluded
  - Ventilation perfusion scan is indicated where available for patients with Normal chest x-ray but Positive D-dimer

Clinical assessment, Chest X-ray and D-dimer testing are crucial where CTPA are not readily available.

Treatment of Venous Thromboembolism

Once the diagnosis of VTE is made, patient should be appropriately counseled on the diagnosis, prognosis and possible complications of the disease. At the same time the available treatment options should be conveyed to the patient together with the cost, likely duration and complications of therapy. Patient should be allowed to make an informed decision on the preferred treatment option.

Treatment modalities for DVT and PE without haemodynamic compromise are essentially the same. The aims of treatment in patients with DVT are to prevent extension and recurrence, prevent or minimize the post thrombotic syndrome and chronic thrombo-embolic pulmonary hypertension. The goal of treatment in PE is to prevent recurrence and death.

Recommendations for the treatment of VTE are based on the strength of evidence from guidelines and expert panel reports already published[20,21].

Available treatment options for VTE could be pharmacological and non-pharmacological.

Pharmacological options

The pharmacological options include the parenteral (heparin, low molecular weight heparin and thrombolytic agents) and the oral anticoagulants (vitamin K antagonists and direct orally active anticoagulants [DOACs]).

Heparins Unfractionated heparin (UFH)

UFH is very heterogeneous in composition and includes molecules varying in chain length (≥ 50 saccharide units) with molecular weight between 5,000-30,000 Daltons. It has no direct anticoagulant effect but acts through anti-thrombin (a serine protease inhibitor whose anticoagulant effect is accelerated by 1000 fold in the presence of heparin). UFH inhibits thrombin by binding to both thrombin and anti-thrombin (AT) to form a ternary complex. Inhibition of activated factor X (FXa) occurs through binding to heparin-AT complex without requirement of heparin binding directly also to FXa.

Initial Steps

Before commencement of heparin the patient's body weight, full blood count (FBC), prothrombin time (PT) and activated partial thromboplastin time (APTT) must be obtained. Also patients should have a baseline platelet count thereafter every 2-3 days starting from 4th day to 14th day of therapy or until heparin is stopped[22].

Indications:

- § Treatment of VTE
- § Because of its short half-life and its complete reversal with protamine sulphate, heparin is preferable in the following conditions:
  - Patients with renal impairment with creatinine clearance (CrCl) of <30ml/min;
  - Patients with an increased risk of bleeding but in whom effective anticoagulation is also required; and
  - Patients on cardiopulmonary bypass.

Dosages:

UFH could be given as a continuous infusion in a fixed dose[23] of 5000 units stat and then 1250-1280 units/h; or weight based[24] of a bolus dose of 80 units/kg followed by 18 units/kg/hour.

It can also be given subcutaneously either as a fixed dose[25] of 333 units/kg stat, then 250 units/kg every 12 hours or adjusted dose[26] of 5000 units stat followed by 17,500 units every 12 h adjusted to aPTT.

Patients that are being treated on outpatient basis could receive subcutaneous UFH at a weight-adjusted dosing (initial dose without monitoring rather than fixed or weight-adjusted dosing with monitoring.

Monitoring

- § Unfractionated heparin is monitored using the aPTT (to achieve and/or maintain a therapeutic ratio of 1.5-2.5 of control plasma) or antiFXa.
- § However, antiFXa is preferable in patients with heparin resistance (patent requires >35,000 IU/24h)*, or prolonged baseline aPTT.
- § Monitoring should be done 6 hourly until 2 consecutive therapeutic results are obtained and 24 hourly thereafter[27].
- § Heparin should be started concurrently with warfarin and continued for at least 5 days after start of warfarin.
- § Some authorities would prefer that heparin be used for up to 72 hours alone before starting warfarin.
- - Heparin should not be discontinued until 2 consecutive therapeutic INR of 2-3 is achieved at least 24 hours apart (but not before day 5 of overlap).

Complications:

- Expectedly, one of the major treatment complications is bleeding.
- In the event of a major bleeding, ** protamine sulfate should be given at a dose of 1mg for every 100 units of heparin infused by slow intravenous (IV) infusion at doses ≤ 5mg/min.

- However, heparin has a relatively short half-life therefore doses administered over the past few hours should only be considered when calculating the dose of protamine sulfate. In emergencies, 25mg of protamine sulfate can be given to patients on continuous heparin infusion and doses repeated if necessary27. Overdose of protamine sulphate is known to predispose to more bleeding by causing platelet aggregation leading to thrombocytopenia. Therefore, care should be taken when calculating the dose.
- Heparin induced thrombocytopenia/ thrombosis (HIT) often times results as a complication of heparin therapy, in about 0.5% (medical patients) - 3 % (after major surgery) of patients. It occurs due to heparin-induced production of antibodies against heparin-platelet factor 4 complexes. Suspected cases should be screened with the 4T (Thrombocytopenia, Timing of Platelet count fall, Thrombosis or other sequelaeand other causesof thrombocytopaenia) pretest. If positive, further use of UFH should be stopped. Since paradoxical thrombosis continues in spite of the thrombocytopenia, anti-coagulation should be continued with either a fondaparinux or DOAC. Argatroban, or danaparoid. Could also be used when available. Note that metabolism of argatroban is liver dependent while that of fondaparinux and danaparoids are kidney dependent. Single case reports do suggest that also DOACs in therapeutic dose can be used as alternative anticoagulant.
- Because of the 10 folds higher risk of heparin-induced thrombocytopenia, unfractionated heparin should not be used for thrombosis prophylaxis, if low molecular weight heparin is available.

Low Molecular Weight Heparin (LMWH)

They are produced by treating heparin chemically or enzymatically to decrease the size of the polysaccharide chains to get a product with restricted mean molecular weight distribution of approximately 4000 to 5000 Daltons (range of 1000-10000 Daltons).

LMWH exerts its anticoagulant effects by inactivating Factor Xa and to a lesser extent activated factor II (FIIa) because the shorter polysaccharide chain does not allow the formation of necessary ternary complex. LMWH have more predictable pharma-cokinetics and a longer half-life than UFH which allows once or twice daily subcutaneous dosing. They are excreted through the kidneys and may accumulate in patients with impaired renal function (enoxaparin > dalteparin > tinzaparin).

Before initiation of LMWH it is necessary to obtain baseline serum creatinine, FBC (with emphasis on platelet count), PT and APTT, and a platelet count.

It is indicated for in-patient/out-patient treatment of acute DVT with or without PE as well as in cancer associated thrombosis (CAT).

Enoxaparin is given at a dose of 1mg/kg 12 hourly subcutaneously or 1.5mg/kg daily. A dose of 1mg/kg daily is used in patients with CrCl of 20-30ml/min. Enoxaparin should be avoided in patients with CrCl of <20ml/min. UFH is the preferred option in patients with CrCl of <20ml/min and patients weighing <40kg[27] .

Dalteparin: is given by subcutaeneous injection, weight based daily dosing of 200 aFXaU/kg b.w. 1x/d for the first month, followed by 150 aFXaU/kg b.w. 1x/d. In case of renal insufficiency that should be reduced by 30%.

LMWH has a more predictable pharma-codynamic profile, wide therapeutic window, and does not require routine coagulation monitoring in clinically stable patients, however there may be need for monitoring in patients with extremes of weight (<50kg and >100kg). Patients on LMWH should be closely monitored for signs and symptoms of bleeding, the FBC and serum creatinine levels should be monitored periodically[27]. Those with low risk of developing complications can be managed as outpatient. Warfarin should be commenced concurrently with LMWH and LMWH continued for at least 5 days. LMWH should not be

discontinued until 2 consecutive therapeutic INR of 2-3 is achieved at least 24 hours apart. If anticoagulation is continued with a DOAC, no overlap treatment is required.

Adverse effects of LMWH

The risk of major bleeding in patients on LMWH in therapeutic dose is about 1-4 %[28]. Once major bleeding or over anticoaguation is observed, LMWH should be discontinued immediately and time to last dose calculated. Protamine sulphate reverses ~60% of anticoagulant activity of LMWH. Before administering protamine sulphate, the severity of bleeding, renal function and the time the last dose was given should be assessed. If the last dose of LMWH is within 8 hours, protamine sulfate should be given at a dose of 1mg per 100 antiFXa units up to a maximum of 50mg (1mg of enoxaparin corresponds approximately to 100 antiFXa units)[29]. A repeat dose of protamine sulfate can be given if bleeding persists or if the APTT is still prolonged 2-4hours after the initial dose of protamine sulfate. If over 8 hours has elapsed before the last administration of LMWH, a lower dose of protamine sulfate may be given (0.5mg per 100 antiFXa units). There is no evidence that administration of protamine sulfate is useful if more than 12 hours have elapsed after the last dose of LMWH.

The second major adverse effect of LMWH is HIT. However, the risk of HIT is 10 times lower for LMWH compared to UFH. Further administration of LMWH should be discontinued in patients who develop thrombocytopenia or thrombosis and treatment continued with alternative anticoagulant (Fondaparinux or DOAC in therapeutic dose). Few patients do have injection site reactions[30].

Fondaparinux

It is a heparin-like anticoagulant with selective antithrombin (AT) dependent antiFXa activity. It is a synthetic pentasaccharide (based on heparin structure) that binds reversibly and with high affinity for AT. It has no direct action on thrombin, its mode of action depends on reducing thrombin generation. Indications include acute VTE and patients with previous history of HIT because cross reactivity with the antibodies responsible for HIT does not occur. As for other anticoagulants, baseline serum creatinine, FBC, PT and APTT should be obtained before commencement of therapy. It is given at a fixed dose of 5mg daily for <50kg, at 7.5mg daily for patients weighing 50-100kg, while >100kg at 10mg daily, all by subcutaneous route. It strongly accumulates in patients with renal insufficiency and should be avoided in patients with CrCl of <30ml/min. Warfarin should be commenced concurrently with fondaparinux and continued for at least 5 days. Fondaparinux should not be discontinued until 2 consecutive therapeutic INR of 2-3 is achieved at least 24 hours apart.

Table 6: Key Recommendations for Use of Heparin in VTE

- § Before initiating anticoagulant therapy, we recommend basic coagulation pro file (PT, APTT,), platelet count, FBC as well as electrolyte, urea and creatinine.
- § Serial monitoring of the platel et count every 2 -3 day starting from day 4 to day 14 of therapy for all patients on heparin.
- § In patients with grossly impaired renal function (CrCl<20 ml/min), UFH is an option for anticoagulation.
- § UFH should be monitored with the APTT and the APTT maintai ned at 1.5 -2.5 of the control plasma.
- § We recommend 6hourly APTT until two consecutive therapeutic results are obtained and thereafter 24hrly.
- § Heparin should be started concurrently with warfarin with overlap period of 5-10days.
- § Heparin should not be discon tinued until at least 2 consecutive therapeutic INR of 2 - 3 has been achieved for at least 24 hours apart or 7 days of heparin depending on which is longer
- § We recommend LMWH for inpatient/outpatient treatment of acute DVT with or without acute PE.
- § Due to th e lack of need for routine monitoring as well as more predictable pharmacodynamics and pharmacokinetics', we recommend LMWH be preferred to UFH except for the indications for UFH stated above.
- § LMWH should be started concurrently with warfarin with overlap period of 5 -10 days. LMWH should not be discontinued until at least 2 consecutive therapeutic INR of 2- 3 has been achieved for at least 24 hours apart.
- § In the event of major bleeding, we recommend that LMWH be discontinued and protamine sulphate be given as stated above

Vitamin K Antagonist (VKA) Warfarin

It's a coumarin derivative. Its mode of action includes inhibition of vitamin K epoxide reductase and vitamin K reductase. There is inhibition of gamma carboxylation required for carboxylation of the coagulation proteins factors II, VII, IX and X, as well as the anticoagulatory proteins C and S. To ensure immediate anticoagulant effect, warfarin therapy must be initiated with a rapidly acting anticoagulant (UFH or LMWH) and after 5 or more days when the necessary anticoagulant effect of warfarin is achieved for most conditions (table below) then the immediate acting anticoagulant can be stopped.

Table 7: Recommended INR Range for different Medical Conditions

Condition	Target INR (Range)
DVT treatment	2.5 (2.0-3.0)
PE treatment	2.5 (2.0-3.0)
DVT prophylaxis	2.5 (2.0-3.0)
Atrial fibrillation	2.5 (2.0-3.0)
Cardiac valve replacement	2.5 (2.0-3.0)
Tissue valves	
Mechanical heart valve	3.0 (2.5-3.5)

Indications: Warfarin is indicated in the treatment and prophylaxis of VTE.

Dosing: Commence warfarin therapy immediately after diagnosis with an initial dose of 5 or 10mg daily. Consider lower doses in the elderly, patients with impaired nutrition, liver failure, congestive heart failure, or with a high risk of bleeding. The dose is then adjusted based on the INR (see Table 7a)

Table 7a: Dose adjustment of Warfarin based on INR

Day	INR	Warfarin dose (mg)
5 mg warfarin initiation normogram		
1		5
2		5
3	<1.5 1.5-1.9 2.0-3.0 >3.0	10 5 2.5 0
4	<1.5 1.5-1.9 2.0-3.0 >3.0	10 7.5 5 0
5	<2.0 2.0-3.0 >3.0	10 5 0
6	<1.5 1.5-1.9 2.0-3.0 >3.0	12.5 10 7.5 0

Monitoring treatment: The anticoagulant effect of vitamin K antagonist is monitored using PT (and/or INR) which is sensitive to decrease in vitamin K dependent factors. The INR is checked daily as from day 3 of warfarin initiation and dosage adjusted until a stable therapeutic effect is achieved[22].

The targeted INR range for most VTE indications is 2-3, and 3.5 for patients with VTE recurrence despite adequate anticoagulation. For patients taking VKA therapy with consistent stable INRs, it is recommended that INR testing frequency should be 6-8 weeks. For patients with previously stable therapeutic INR values presenting with a single out of range INR of ≤ 0.5 should be re-checked within 1-2 weeks without adjusting the dose. INR should be checked every 6-8 weeks (4-6 weeks for mechanical valves) and only if INR values are stable. A higher INR is recommended for patients with mechanical heart valve replacement and those with failed anticoagulant therapy despite well-documented INR values in range of 2-3.

Complications: The most serious complication of vitamin K antagonists is bleeding which is related to patients' characteristics, intensity of anticoagulation and the length of therapy. Other side effects include skin necrosis, purple toe syndrome, rash and hepatitis. Anticoagulation must be reversed for episodes of bleeding, surgery, trauma or drug overdose as shown in the table below. Serious bleeding and major overdose may require factor replacement and intravenous administration of vitamin K.

Table 8: Recommendations on the Management of Bleeding and Excessive Anticoagulation by the British Committee for Standards in Haematology (third edition 1998; 2005 update).

INR	Dose Adjustment
4. 0-6.0	Reduce warfarin dose or stop
6.0-8.0	Stop warfarin*
No bleeding or minor bleeding	Restart warfarin when INR <5.0
>8.0	Stop warfarin*
No bleeding or minor bleeding	Restart warfarin when INR <5.0 If other risk factors for bleeding give 0.5-2.5 mg vitamin K orally
Major bleeding	Stop warfarin FFP 15 mL/kg (when available), OR Give 5 mg vitamin K (i.v. or oral)

*1 mg vitamin K may be given orally to rapidly reduce the INR to the therapeutic range within 24 hours in all patients with an INR above the therapeutic range and no bleeding.

Non-Pharmacological Options in the Management of VTE

- § We recommend that warfarin be started immediately after diagnosis at a dose of 5mg daily.
- § A target INR of 2-3 should be maintained for most indications and an INR of 2.5- 3.5 for patients on mechanical heart valves and 3.5 for recurrent VTE despite anticoagulation INR should be checked daily as from day 3 of warfarin initiation and dosage adjusted until a stable therapeutic value has been achieved.
- § We recommend 4-6 weekly PT/INR in all patients on warfarin who have consistently stable INR
- § We recommend that physicians be familiar with table 8 above in managing bleeding complications associated with warfarin.

Direct Orally-active Anticoagulants (DOACs)

The availability of DOACs in Nigeria has impacted positively in the management of VTE as well as AF. Currently the licensed DOACs include rivaroxaban, dabigatran, apixaban and edoxaban. Several studies showed that DOACs exhibit a comparable efficacy and a significantly lower bleeding risk when compared with warfarin[32, 33]. The advantages of these drugs include:

- § They can be administered once or twice daily without need for monitoring.
- § They have fewer clinically related drug interactions
- § They have fast onset of action like the LMWH and can replace these parenteral agents.
- § Initial heparin anticoagulation not required for rivaroxaban but initial higher doses of anticoagulant must be given in the first few weeks of therapy.

Rivaroxaban

Mechanism of action: Rivaroxaban acts by direct inhibition of FXa and achieves maximum plasma levels approximately 3 hours after oral ingestion. Once at steady state, the terminal half-life is 4 to 9 hours (up to 12 hours in patients 75 years old). It has very few significant drug-drug interactions, and food does not affect absorption from the gastrointestinal tract; the oral bioavailability is more than 80%[34].

Indications:

- § Prevention of VTE in orthopaedic patients who have undergone elective total hip replacement or total knee replacement surgery
- § Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- § Treatment of DVT and PE.
- § Reduction in the risk of recurrence of DVT/PE.

Dosage:

- § For orthopaedic prophylaxis: 10 mg po qday (12-14 days for knee replacement and 35 days for hip replacement)
- § For Atrial Fibrillation: 20 mg po qday or 15 mg po qday if CrCl 30-49 mL/min
- § For treatment of VTE: 15 mg po BID for 3 weeks, followed by 20 mg po qday or followed by 15 mg po qday if CrCl 30-49 mL/min

Contraindication: Severe renal failure (CrCl < 30 mL/min)

Direct Orally-active Anticoagulants (DOACs)

Monitoring: No anticoagulation monitoring required, possible by aFXa test.

Reversal agent (antidote): Andexanet alfa is still awaiting FDA approval.

Switching between rivaroxaban and other anticoagulants[35]:

- **Conversion from warfarin to rivaroxaban:** initiate rivaroxaban when INR < 3 to avoid inadequate anticoagulation.
- **Conversion from rivaroxaban to warfarin:** No clinical trial data are available to guide converting patients from rivaroxaban to warfarin. One approach is to initiate warfarin and LMWH 24 hours after discontinuation of rivaroxaban and continue LMWH until the INR is in the therapeutic range. Note that rivaroxaban affects INR and the initial INR measurement may be unreliable.
- **Conversion from continuous infusion heparin to rivaroxaban:** Initiate rivaroxaban at the time of heparin discontinuation.
- **Conversion from rivaroxaban to continuous infusion heparin:** Initiate continuous infusion heparin 24 hours after discontinuation of rivaroxaban. Conversion from other anticoagulants to rivaroxaban: Discontinue anticoagulant and initiate rivaroxaban ≤ 2 hours prior to the next regularly scheduled evening dose of the discontinued anticoagulant.
- **Conversion from rivaroxaban to other anticoagulants (other than warfarin):** Initiate the anticoagulant 24 hours after the discontinuation of rivaroxaban.

Dabigatran

Mechanism of action: Dabigatran directly inhibits both free and clot-bound thrombin. It is rapidly absorbed orally and reaches peak plasma levels 1.5 hours after ingestion. Once at steady state, dabigatran has a half-life of 14 to 17 hours. With oral treatment, bioavailability is 72%, and dabigatran is predominantly excreted in the faeces[36].

Indications:

- Treatment of acute VTE
- Indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Prevention of VTE in patients who have undergone elective total hip replacement or total knee replacement surgery.

Dosage:

- Acute VTE: 150 mg BID after 5-10 days of parenteral anticoagulation
- Atrial fibrillation:
  - 150 mg po BID or
  - 110 mg po BID if age > 75 years or in patients with increased risk of bleeding
- Hip replacement surgery: 220 mg po qday or 150 mg po qday if age > 75 years to be commenced within 4 hours of surgery for 28-35 days post-op.
- Knee replacement surgery: 150 mg po qday to be commenced within 4 hours of surgery for 28-35 days post-op.

Contraindication:

- Severe renal failure (CrCl < 30 mL/min); and
- Caution for patients with moderate renal impairment (CrCl 30-50 mL/min).

Monitoring:

- No routine anticoagulation monitoring is required
- **Thrombin Time** (TT): TOO SENSITIVE but a normal TT assures that there is no remaining anticoagulant effect of dabigatran.
- Dilute Thrombin Time: can be used to monitor dabigatran (this test is not available in Nigeria)
- **aPTT/ PTTK:** INSENSITIVE: If prolonged, then there is significant drug

present. However, a normal aPTT does not necessarily mean there is no effect of dabigatran.

Reversal agent (antidote): Idarucizumab is used in reversing the effect of dabigatran effectively within few minutes of administration.

Switching between dabigatran and other anticoagulants[35]:

- **Conversion to dabigatran from a continuous infusion anticoagulant (e.g. heparin):** Administer dabigatran at time of discontinuation of infusion
- **Conversion to dabigatran from a parenteral anticoagulant (e.g. LMWH, enoxaparin):** Administer dabigatran at 0-2 hours prior the next scheduled dose of parenteral anticoagulant
- **Conversion to dabigatran from warfarin:** Initiate dabigatran when INR < 2
- **Conversion to continuous infusion anticoagulant (e.g. Heparin) from dabigatran:** commence 12 hours after the last dose of dabigatran if CrCl is >30 ml/min.
- **Conversion to warfarin from dabigatran:**
  - CrCl>50 ml/min: commence warfarin 3 days prior to dabigatran discontinuation
  - CrCl 31-50 ml/min: commence warfarin 2 days prior to dabigatran discontinuation.

Apixaban:

Apixaban is a direct inhibitor of Factor Xa (both within and outside the prothrombinase complex). It has more than 50% bioavailability and reaches peak plasma concentration in 3 to 4 hours after oral administration. The terminal half-life is 10 to 14 hours after repeated doses. Apixaban is metabolized in part by CYP3A4; it is partly eliminated by the kidneys (25%) and, to some extent, also processed via CYP-independent mechanisms in the liver.

Indications:

- Prevention of stroke and systemic embolism in non-valvular atrial fibrillation
- Prevention and treatment of VTE

Dosing:

- Treatment of DVT/PE – initial dose of 10mg BID for 7 days then 5mg BID.
- 2.5mg BID in patients with any 2 of the following:
  - Serum creatinine ≥ 1.5 mg/dL,
  - Age ≥ 80 years
  - Body weight ≤ 60 kg.

Monitoring: Routine monitoring is not recommended, possible by aFXa test.

Reversal agent (antidote): Andexanet alfa is still awaiting FDA approval.

Switching between apixaban with other anticoagulants[34]

- **Conversion from warfarin to apixaban:** Discontinue warfarin and initiate apixaban when INR is < 2.
- **Conversion from apixaban to warfarin:** Apixaban affects the INR; measuring the INR during co-administration with warfarin therapy may not be useful for determining an appropriate dose of warfarin. If continuous anticoagulation is necessary, discontinue apixaban and begin both a parenteral anticoagulant with warfarin when the next dose of apixaban is due; discontinue parenteral anticoagulant when INR reaches an acceptable range.
- **Conversion between apixaban and other non-warfarin anticoagulants:** Discontinue anticoagulant being taken and begin the other at the next scheduled dose.

Edoxaban:

Mechanism of action: directly inhibits Factor Xa.

Indications:

- § Prevention of stroke and systemic embolism in non-valvular atrial fibrillation
- § Prevention and treatment of VTE.

Dosage:

- § 60 mg once daily after 5-10 days of parenteral anticoagulation for >60kg body weight.
- § 30 mg once daily if CrCl 30–50 mL/min or weight <60 kg
- § Contraindicated if CrCL is <30ml/min.

Monitoring: not routinely required, possible by aFXa test.

Reversal agent (antidote): Andexanet alfa is still awaiting FDA approval.

Switching between edoxaban and other anticoagulants[34]:

- § **Conversion from edoxaban to warfarin:** discontinue edoxaban and start warfarin at the scheduled time for the next dose.
- § **Conversion from edoxaban to parenteral anticoagulants:** discontinue edoxaban and start parenteral anticoagulants at the scheduled time for the next dose.
- § **Conversion to edoxaban from warfarin:** discontinue warfarin and start edoxaban when INR is≤ 2.5.
- § **Conversion to edoxaban from LMWH:** discontinue LMWH and initiate edoxaban at the time of the next scheduled dose of LMWH.
- § **Conversion to edoxaban from UFH:** discontinue UFH infusion and initiate edoxaban 4 hours later.

Key Recommendations for Use of Direct Oral Anticoagulants in VTE

We recommend that for all patients with appropriate indications, the availability, cost, advantages and disadvantages of DOACS should be made known to them.

Thrombolytic Agents

It is indicated in patients with PE presenting with evidence of vascular collapse/ haemodynamic compromise (hypotension or syncope) or for selected patients with PE who have clinical findings of right ventricular failure or echocardiography evidence of right ventricular hypokinesia. It provides more rapid lysis of PE and more rapid restoration of right ventricular function and pulmonary perfusion than does anticoagulant treatment.

Thrombolytics are indicated in patients with acute PE with haemodynamic instability to reduce the thromboembolic burden and resistance in the pulmonary circulation with improved gaseous exchange as well as right ventricular function[37]. There are basically 4 types of thrombolytic which include the tissue plasminogen activator, streptokinase, urokinase and anistreplase[38]. Of all these streptokinase and urokinase are available in Nigeria. Their use and dosage depend on the indication but are generally given intravenously either systemically as in PE or via catheter directed means as in DVT of the extremities[20, 37]. To be most effective, it is recommended they are given within 30 min of presentation to the hospital[38].

Streptokinase should be given at a loading dose of 220,000IU and a maintenance dose at 100,000 IU per hour over a period of 24-72 hours. It is indicated in VTE and arterial thromboembolism. On the other hand, tPA is indicated only for PE at an effective dose of 100mg intravenous infusion over 2 hours.

Urokinase is also only indicated for PE and given in a loading 2000 IU over 10 minutes and maintained with 2000 IU per hour over 12 hours. In all, concurrent administration of heparin is unnecessary.

Absolute Contraindications to Thrombolytic Therapy of PE:

1. Haemorrhagic cerebrovascular accidents (CVA)
2. Intracranial neoplasia, recent cranial surgery or trauma within 10 days
3. Uncontrolled severe hypertension because of an increased risk of intracranial bleeding.
4. Major thoracic or abdominal surgery within 10 days
5. Prolonged cardiopulmonary resuscitation
6. Current severe bleeding from gastro-intestinal tract (GIT) or other organs

Thrombolytic Agents

Complications of thrombolytic therapy:

Major bleeding, in the event of which thrombolytic agent should be stopped, plasma and tranexamic acid administered. Fibrinogen should be assayed for possible replacement. Other complications include allergy and embolism.

§ We recommend the use of thrombolytic agents in patients with acute PE with haemodynamic compromise

Non-Pharmacological Options in the Management of VTE

Inferior Vena Cava Filter (IVC)

The placement of an IVC filter should be handled very carefully and only in patients with acute VTE who have an absolute contraindication to anticoagulant therapy, complication of anticoagulation leading to cessation of therapy or failure of anticoagulation. IVC filters are not recommended in patients with free floating thrombus, prior to systemic thrombolysis, surgical thrombolectomy or pulmonary thrombo-end-arterectomy. Filters are either temporary or permanent and are usually placed in the infra renal portion of the inferior vena cava.

Permanent filter should be used only with great caution. Its use results in an increased incidence of recurrent DVT after 1 to 2 years of insertion, where indication for it is transient a retrievable/temporary vena cava filter should be used and should be evaluated periodically for filter retrieval. Pharmacological anticoagulation should be resumed in patients with IVC filter once contraindications to anticoagulation or acute bleeding complications have resolved[39].

Compression Stockings

It is designed and worn around the leg, they are elastic and compress the limb thereby helping to prevent occurrence and guard against further progression of venous thrombus. The mechanism of action remains unclear though it is thought to reduce the diameter of distended veins and increase venous flow velocity and valve effectiveness. Hence, they help prevent late complications like venous insufficiency and PTS.

There are two types: gradient compression stocking and anti-embolism compression stocking. Both are designed to remedy impaired musculo-venous pump performance caused by incompetent leg veins. Compression is highest around the ankle and lessens towards the top of the hose. It is recommended to be worn in the day time for a minimum of 12 months unless for asymptomatic distal DVT. Compressive stockings are the most popular physical method of DVT prophylaxis. It is not as effective as anticoagulant or intermittent compression devices [40], furthermore, its elasticity and effectiveness is lost with time and should be replaced every 6 months.

Compressive stockings are not recommended for use in patients who experience much pain and have severe arterial insufficiency with intermittent claudication.

Intermittent pneumatic compression device (IPCD) is a therapeutic technique used in medical devices that include an air pump and inflatable auxiliary slips, gloves or boots in a system designed to improve venous circulation in the limbs of patients who suffer oedema or at risk of VTE. The functional aim of the IPCD is to pump blood from the underlying deep veins with

assumed competent valves. It ensures continuous movement of venous blood in the circulation. In high risk surgical patients consider the use of IPCD until bleeding risk diminishes. The main disadvantages of IPCD over anticoagulants are those of application and patient compliance. IPCD can only prevent stasis only when applied to the limb. It can be used before, during and after surgery. Duration of Treatment for VTE

Key Recommendations

That patients with provoked VTE should be treated for 3 months

That patients with unprovoked VTE should be treated for 6 months

That patients with inherited thrombophilia with previous VTE should be considered for long term anticoagulation if no contraindications

That patients on anticoagulant should be regularly assessed for bleeding and other complications

Cancer-associated thrombosis (CAT)

Cancers are associated with increased risk of thrombosis and chemotherapy further increases this risk. Venous thromboembolism occurring in cancer patients is one of the leading causes of death in cancer patients and is associated with worsened survivals. Patients with VTE and cancer should be treated with LMWH for the first 3-6 months and the patient should receive anticoagulation indefinitely or until cancer resolves. People with unprovoked or non-surgically related VTE and who are not known to have cancer should be timely investigated for cancer.

Thromboprophylaxis

Venous thromboembolic (VTE) disease is a significant cause of morbidity and mortality in hospitalized and surgical patients. There is very limited study on VTE risk in Nigerians with medical and surgical illnesses. Data from Epidemiologic International Day for the evaluation of outcomes research in Arica (Endorse Africa) have shown that 62.2% of medical patients and 43.8% of surgical patients are at risk of VTE41. Venous thromboembolism is (partly) preventable and all hospital inpatients should be risk assessed for VTE upon admission. Appropriate use of thromboprophylatic agents in at risk individuals have the advantage of reducing morbidity and mortality, hospital stay as well as overall cost of treatment. Available options include pharmacological or non- pharmacological agents. Pharmacological agents are the traditional anticoagulants (LMWH, vitamin k antagonists) and more recently DOACs. Non-pharmacological agents include mechanical devices which could be surgical (inferior vena cava filters) or non-surgical (graduated compression stockings –GCS or Antiembolism stocking (AES), pneumatic compression devices- PCD and foot pumps) others include early mobilization. The later should be encouraged, as it does not involve any additional cost.

Risk Assessment for Venous Thrombo-embolism and Bleeding Risk

- § Risk assessment is an important tool for preventing VTE and it should be patient specific. Some specialties have risk assessment tools and the commonly used bleeding risk assessment is the HASBLED Score.
- § All hospitalized patients should have a risk assessment for VTE, the risk documented and discussed with the patient and thromboprophylaxis offered. Patients on admission should be reassessed 24 hours after admission and every time the clinical situation changes.

Using Thromboprophylaxis

Thromboprophylaxis in Medical Patients

The risk of DVT in medically hospitalized patients without anticoagulation is about 10-20%. The ENDORSE Study showed that 42% of medical inpatients are at significant risk for

VTE and only about 40% of them receive appropriate prophylaxis [42]. It is usually associated with reduced mobility, age > 70years, heart or respiratory failure, acute MI or ischemic stroke, acute infection or rheumatologic disorder, obesity etc as in the Padua Prediction Score.

§ A risk assessment model for thrombophylaxis in the medical patient should be able to identify patients who are at a significant risk of VTE and therefore would benefit from thromboprophylaxis and those in whom thromboprophylaxis is contraindicated.

§ Before a decision to offer pharmacological prophylaxis, bleeding risk assessment must be carried out.

Table 9: Padua Risk Assessment Score for Medical Patients

Risk Factor	Points
Active cancer	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility	3
Already known thrombophilic condition	3
Recent (> 1 mo) trauma and/or surgery	2
Elderly age (>70 y)	
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI >30)	1
Ongoing hormonal treatment	1

Table 10: VTE Prophylaxis Recommendations Based on Risk Score

Points	Risk	Recommendation
<4	Low VTE Risk	VTE prophylaxis not needed
>4	High VTE Risk and Low Bleed Risk	Pharmacologic Prophylaxis
	High VTE Risk and High Bleed Risk	Mechanical Prophylaxis

Table 11: Bleeding Risk Factors

Patient related
§ Active bleeding § Acquired bleeding disorders (such as acute liver failure) Significantly impaired liver function (INR>1.4) Impaired renal function (creatinine clearance<30mL/min) § Concurrent use of anticoagulants known to increase th e risk of bleeding (such as warfarin with INR > 2) § Acute stroke § Thrombocytopaenia (platelets < 75 x 109/l) § Uncontrolled hypertension (≥ 230/120 mmHg) § Untreated inherited bleeding disorders (such as haemophilia or von Willebrand's disease)
Admission related
§ Neurosurgery, spinal surgery or eye surgery § Other procedures with high bleeding risk § Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours or expected within the next 12 hours

§ For patients with high risk of bleeding, non-pharmacological means of thrombo-prophylaxis is recommended, these include AES, IPC and patients with stroke are not recommended to use AES in the acute phases of stroke.

§ LMWH has proven to be safe in medical patients who do not have a significant bleeding risk.

§ UFH is safer for patients with renal insufficiency (CrCl <30mL/min)

Risk assessment model and thromboprophylaxis for the medically ill patient (Adapted from Cohen et al and Southampton University Hospital VTE guidelines)

Is the patient >40 years? Is mobility going to be significantly reduced? Is there presence of any of these conditions? Acute MI, HF, cancer, sepsis, rheumatic disease, respiratory failure, ischaemic stroke, obesity (BMI 30kg/m^2)

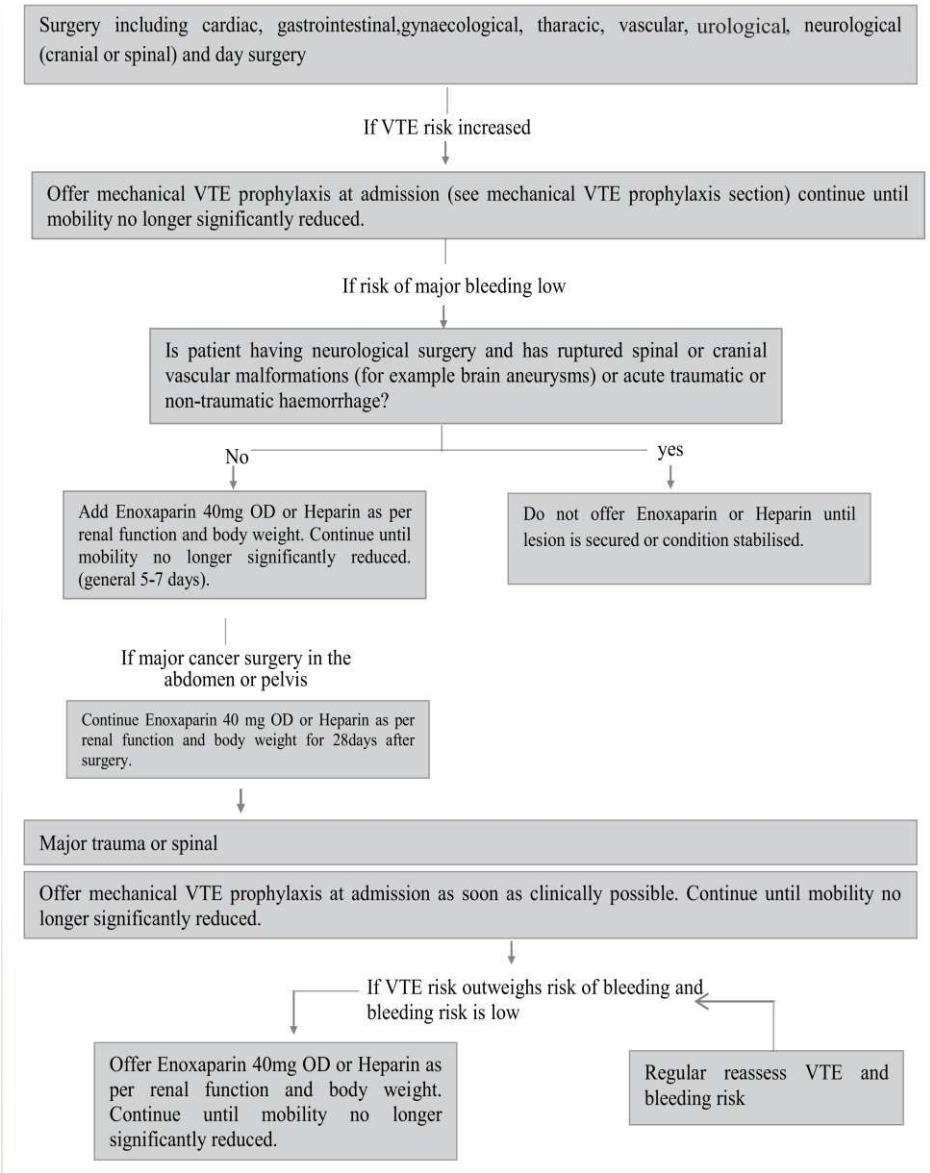


Figure 7: An Algorithm for Risk Assessment and Thromboprophylaxis for the Medically Ill Patients (adapted from Cohen *et al* and Southampton University Hospital, VTE Guidelines)

Enoxaparin is preferred because of evidence based increased safety profile (see contraindication to enoxaparin above) MI; myocardial infarction, HF; Heart failure LMWH: Low molecular weight heparin, VTE, venous thromboembolism, AES: Anti-embolism stockings

Key Recommendations for VTE Prophylaxis In TheMedical Patient

- § We recommend that all hospitalized patients should have a risk assessment for VTE and bleeding risk upon admission, the risk should be documented and discussed with the patient and thromboprophylaxis offered (Note that scores especially the bleeding risk score are quite crude and may not predict very well)
- § That patients on admission should be reassessed 24 hours after admission and every time the clinical situation changes.
- § We recommend that patients at high risk of bleeding should be offered mechanical prophylaxis
- § That patients at high risk of VTE and low bleeding risks should be offered LMWH
- § That thromboprophylaxis should continue as long as the risk persists if no contraindication

In Surgical Patients

The risk of VTE in surgical patients varies according to patient-related factors and procedure-related factors. The risk for VTE in surgical patients has been quoted to be as high as 59%[42]The Caprini Score can be used to assess the risk of surgical patients for VTE .[43] Thromboprophylaxis has been shown to be effective. However, it is associated with adverse effects, additional financial burden and some inconvenience to the patient. It is therefore necessary to make a balanced judgement for each patient. When making a decision to offer thromboprophylaxis consideration should be given to patient's risk, procedure related risk and the efficacy, safety, cost and convenience of the prophylaxis method[44,45] as well as patient's preference. The risk factors for VTE in the surgical patient are the same as the general risk factors outlined in Table 1 above. Mechanical or pharmacological thromboprophylaxis could be used for the surgical patient depending on whether or not there is contraindication to pharmacological thromboprophylaxis

Table 12: Recommended Thromboprophylaxis for Surgical Patients

Thromboprophylaxis Type	**Patient Type (excluding day case)**
Mechanical (GCS, IPC, foot pump devices)	All surgical patients
LMWH	Surgical patients with one or more patient related risk factors with no contraindication to thromboprophylaxis

Table 13: Caprini Risk Assessment Score for Surgical Patients [43]

1 Point	2 Points	3 Points	4 Points
Age 41-60 y	Age 61-74 y	Age >75 y	Stroke (<1 mo)
Minor surgery	Arthroscopic surgery	History of VTE	Elective arthroplasty
BMI >25 kg/m2	Major open surgery (>45min)	Family history of VTE	Hip, pelvis, or leg fracture
Swollen legs	Laparoscopic surgery (>45 min)	Prothrombin 20210A	
Varicose veins	Malignancy	Lupus Anticoagulant	
Pregnancy or Postpartum	Confined to bed (>72 h)		
History of unexplained or recurrent spontaneous abortion	Immobilizing plaster cast	Anticardiolipin antibodies	
Oral contraceptives or hormone replacement Sepsis (<1 mo)	Central venous access	Elevated serum Homocysteine Heparin-induced Thrombocytopenia	
Serious lung disease, including pneumonia (<1 mo)		Other congenital or acquired thrombophilia	
Abnormal pulmonary Function			
Congestive heart failure (< 1 mo)			
History of inflammatory bowel disease			
Medical patient at bed rest			

Table 14: Recommended Prophylaxis Based on Caprini Score

Caprini Score	Risk of VTE	VTE Incidence (%)	Recommended Prophylaxis
0 – 2	Very low – low	<1.5%	Early ambulation, IPC
3 – 4	Moderate	3	LMWH, UFH, or IPC. If high bleeding risk, IPC until bleeding risk diminishes.
5 – 8	High	6	LMWH+IPC or UFH+IPC. If high bleeding risk, IPC until bleeding risk diminishes.
>8	Very high	6.5 –18	LMWH+IPC or UFH+IPC. If high bleeding risk, IPC until bleeding risk diminishes. Consider extended duration prophylaxis.

**Abdominal or pelvic surgery for cancer should receive extended VTE prophylaxis with LMWH for 30 days*

Patient-related factors that increase the risk of VTE in surgical patients include age >60 years, past history of VTE, immobility before surgery, underlying cancer, pregnancy, oestrogen therapy, obesity, HIV/AIDS, inherited thrombophilic states. Procedure- related risk factors that are associated with VTE include duration of procedure, degree of tissue damage, and degree of immobility after surgery and type of surgery. For low risk procedures/minor surgeries with no patient-related factors, early mobilization is recommended.

For high risk procedures/ major surgeries with or without patient related risk factors, any of the following pharmacological thromboprophylaxis are recommended:

- § Enoxaparin 40mg SC daily
- § Dalterparin 0.4ml SC daily

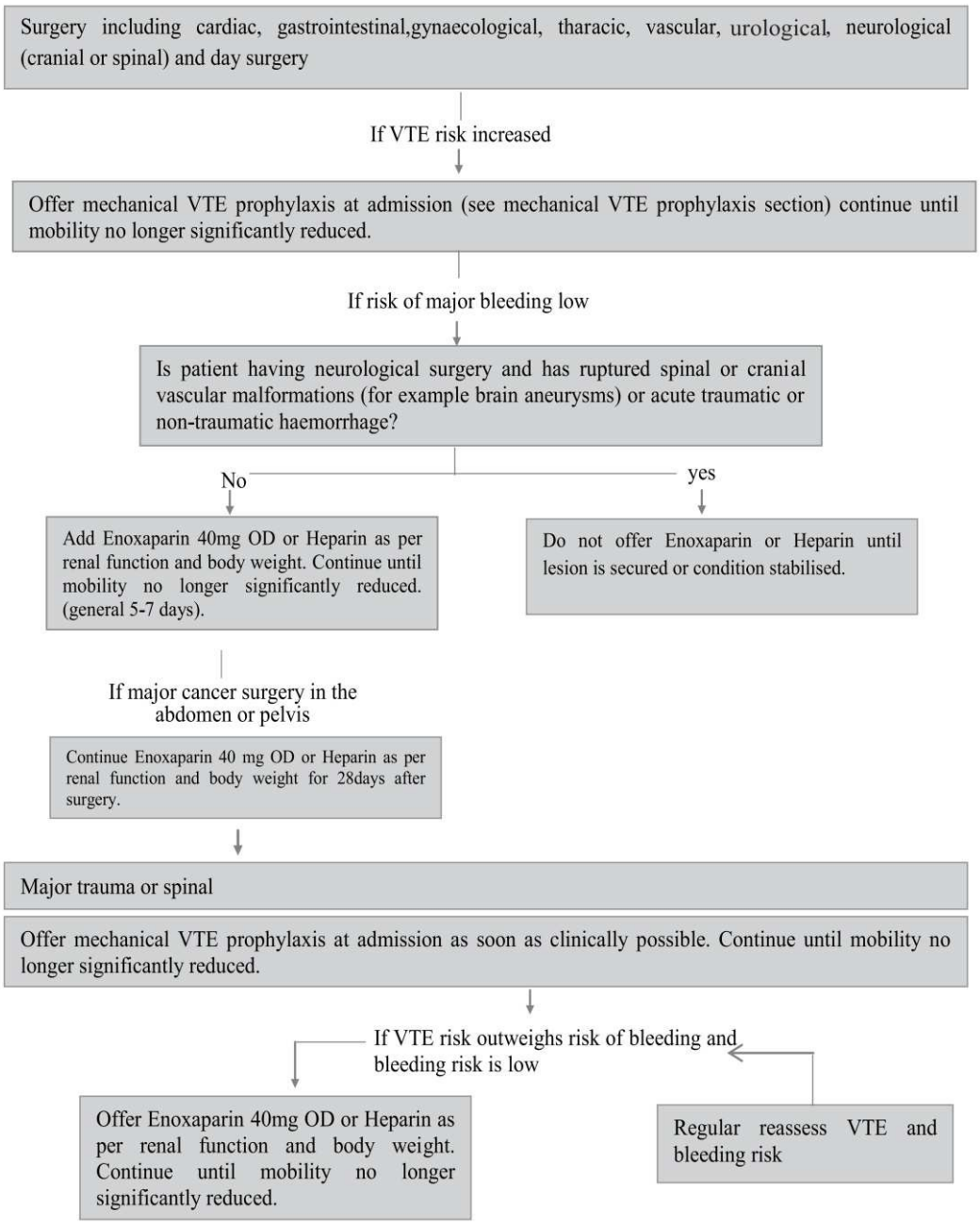


Figure 8: A Risk Assessment Model for Surgical Patients
(Adapted from Southampton University Hospital, VTE Guidelines)

Key Recommendations for VTE Prophylaxis in the Surgical Patient

- § We recommend that all hospitalized patients should have a risk assessment for VTE and bleeding risk upon admission, the risk should be documented and discussed with the patient and thromboprophylaxis offered (Note that the value of these assessment may not be absolute)
- § That patients on admission should be reassessed 24 hours after admission and every time the clinical situation changes.
- § That patients at very low risk of VTE, be offered mechanical thromboprophylaxis and early ambulation encouraged
- § That both mechanical and and pharmacological (LMWH) should be offered to patients at moderate to high risk of VTE
- § UFH should be used for thrombo-prophylaxis in patients with severe renal impairment (CrCL <30ml/min)
- § Patients with pelvic or abdominal surgery as a result of cancer should have extended prophylaxis (up to 4 weeks)

In Orthopedic Patients

Orthopedic patients are at very high risk for VTE, due to prolonged immobilization before surgery and long duration of surgical procedures. The risk of VTE in orthopedic surgery depends on the type of procedure. Little or no risk is documented with hand or wrist surgery while very high risk is associated with total hip or knee replacement surgery due to prolonged immobility before surgery and long duration of surgical procedures. The rate of symptomatic deep vein thrombosis in total hip replacement surgery is about 4% while the rate of fatal pulmonary embolism is 0.2% in the absence of prophylaxis[44].

In patients with lower limb casts, the incidence of DVT is about 1.1% to 40%[21,45] the higher percentage being asymptomatic with a chance of propagation and PE.

There is evidence that LMWH (UFH in those with renal insufficiency) is safe to prevent

DVT in orthopedic patients with prolonged immobilization by casts or braces[44].

Patients with lower limb casts should be risk assessed for pharmacologic thrombo-prophylaxis and the risk discussed with the patient. Patients should use prophylaxis till casts are removed.

In patients undergoing hip fracture surgery or total hip or knee replacement surgery, we recommend the use of LMWH, low-dose UFH, Rivaroxaban, Dabigatran, dose adjusted VKA and aspirin over no antithrombotic[22].

These antithrombotic agents should if commenced before the surgery be stopped before surgery (eg LMWH >12 hours before surgery).

Key Recommendations for Orthopedic Patients

- § That persons with fractures of the hip, pelvis or proximal femur should be offered LMWH commencing 6-12 hours post-surgery if VTE risk is more than bleeding risk
- § That patients with lower limb immobilization should be offered LMWH if VTE risk outweighs bleeding risk. Stopping prophylaxis should be considered if immobilization exceeds 6 weeks
- § That patients with elective hip or knee replacement surgery should be offered LMWH for 10 days followed by aspirin 75-150mg OD for a further 28 days or LMWH for 28 days, or Rivaroxaban or Dabigatran depending on patient's preference or availability (see section on DOAC above)

In Cancer Patients

Patients that have malignancies are 6 times more likely to have VTE than their counterparts

without cancer, it also accounts for more than 20% of new cases of VTE[46]. Cancer associated thrombosis is also the second leading cause of death in cancer patients[47]. Concerns about cancer-associated thrombosis is not only for the increased morbidity and mortality but also for the challenges of management. Cancer is a risk factor for bleeding, certain chemo-therapeutic agents are thrombogenic while a number reduce the platelet count with an attendant increased predisposition to bleeding, furthermore chronic anticoagulation also increases the potential for bleeding making full anticoagulation difficult in the event of thrombosis while interruption of anticoagulation also potent the danger of recurrence[45]. Therefore, patients with cancer must be properly risk assessed to identify those in whom prophylactic anticoagulation is necessary. The risk factors for VTE in cancer patients are listed on Table 15. They include patient related, cancer related and treatment related risk factors.

Table 15: Patient Related Risk Factors

§ *Age (incidence increases with age)* § *Race (higher incidence in American blacks and lower in Asians)* § *Medical comorbid conditions* § *Obesity (BMI>30kk/m2)* § *Previous thrombosis* § *Varicose veins*
Cancer related risk factors § *Site of cancer (higher in pancreatic, gastric, primary brain tumours, lung,* § *renal, lymphomas)* § *Stage of cancer (higher in advanced stage disease)* § *Grade of tumour (higher in high-grade tumours)* § *Time after initial diagnosis (higher in the first 3-6 months)*
Treatment related risk factors § *Immunomodulatory agents (thalidomide, lenalidomide, homonal therapy* § *like tamoxifen))* § *Transfusions* § *Erythropoietin stimulating agents* § *Radiation* § *Inferior vena cava filters* § *Thrombocytosis (platelet count>350000/mm3)* § *Anaemia (Hb<10g/dl)* § *Elevated white cell count (>11000/mm3)* § *Major surgical resection* § *Increased levels of FVIII*

The Khorana risk assessment model has been externally validated. It is a simple tool that could be used in making decisions on the need for thromboprophylaxis.

Table 15a: Risk Score for the Prediction of VTE in Cancer Patients [48]

	Points
Very high risk (stomach, pancreas, primary brain tumour	2
High risk (lung, kidney, bladder, testicular, lymphoma, gynaecological malignancies	1
Pre - chemotherapy platelet counts 350000/µl	1
Haemoglobin level <10g/dl (or use of erythropoietin	1
Pre-chemotherapy leucocyte count>11000/ µl	1
	1

Total score = 0 indicates low risk, score= 1-2 is assigned intermediate risk and score= ≥ 3 is high risk (rates of VTE in the validation cohort: low risk 0.3%, intermediate risk 2% and 6.7% in high risk.

Aside the Khorana score, there is a risk assessment algorithm developed by the International Multiple Myeloma Working Group for patients with multiple myeloma. These patients are particularly at risk not only because of the cancer but also from the use of immunomodulatory drugs and combination chemotherapy used in its management[49]. Though not clinically validated, it's an expert document which could be adapted for prophylactic anticoagulation in Nigeria.

Table 16: Risk Assessment for Myeloma Patients on Therapy
(adapted from the recommendations of the International Myeloma Working Group)

Individual risk factors § Obesity § Previous history of VTE § Central venous catheter or pacemaker
Associated disease § Cardiac disease § Chonic renal disease § Diabetes § Acute infection § Immobilization
Myeloma-related risk factors: § Diagnosis § Hyperviscosity
Myeloma therapy: § High dose dexamethasone § Doxorubicin § Combination chemotherapy and the use of immunomodulatory agents
General surgery Anaesthesia Trauma Erythropoietin use Blood clotting disorders
0-1 Risk factor present: Aspirin 81 – 325 mg once daily. **≥2 Risk factor: LMWH (enoxaparin 40mg daily OR full dose warfarin (target INR 2-3)**

Treating cancer associated thrombosis is associated with a significant risk for bleeding, interruption of cancer treatment and recurrence of VTE[50].

Key Recommendation for Thrombo-prophylaxis of Cancer Patients

- *That Khorana score has been clinically validated and may be used to risk assess cancer patients*
- *We recommend that hospitalized patients with active malignancy and acute medical illness or reduced mobility should receive pharmacologic thromboprophylaxis in the absence of contraindications.*
- *In the absence of additional risk factors, hospitalized patients with cancer may be considered for VTE prophylaxis.*
- *Patients with cancer undergoing abdominal surgery should commence UFH or LMWH before surgery.*
- *Patients with multiple myeloma on therapy should receive thrombo-prophylaxis with aspirin or LMWH in low-risk patients and LMWH in high risk patients*[51].

Management of VTE in Pregnancy - Key Recommendations[52]

- *Pregnant women diagnosed with a VTE should be treated with full dose LMWH (e.g. enoxaparin 1.5 mg/kg/q day) for the remainder of their pregnancy.*
- *Patients should complete a minimum 3 months of anticoagulation including treatment throughout pregnancy and 6 weeks post-partum.*
- *Warfarin is contraindicated during the first trimester of pregnancy because of the risk of teratogenicity.*
- *Primary prophylaxis (with prophylaxis doses of LMWH) is reserved for thrombophilic women during the six weeks post-partum.*
- *Secondary prophylaxis with prophylaxis doses of LMWH) during pregnancy is indicated in women who have a previous history of an unprovoked VTE, a VTE associated with estrogen use, pregnancy, and/or obesity or a VTE associated with a thrombophilia.*
- *All pregnant women with prior VTE, we suggest postpartum prophylaxis for 6 weeks with prophylactic or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0.*
- *Anticoagulation post-partum can be either warfarin or LMWH, as neither is excreted in breast milk and both are safe for the new-born.*

Thrombosis in the Setting of a Lupus Anticoagulant

- All venous and arterial thrombotic events in the setting of a lupus anticoagulant or an anticardiolipin antibody should be treated with lifelong warfarin therapy, maintaining an INR of 2.0-3.0.

Recurrent Foetal Loss[52]

- Women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation), should be screened for APLAs.
- Women with recurrent fetal loss, defined as at least three 1st trimester losses, two 2nd trimester losses or one 3rd trimester loss in the setting of a positive lupus anticoagulant or anticardiolipin antibody should be treated throughout the pregnancy with prophylactic LMWH dose (either dalteparin 5000 units sc qday or enoxaparin 40 mg po qday) combined with ASA 75mg po qday for all subsequent pregnancies.

Atrial Fibrillation

A. Indications for indefinite anticoagulation therapy in Atrial Fibrillation:

- Paroxysmal, persistent, or permanent atrial fibrillation or atrial flutter
- Patients should initially be stratified for stroke risk and bleeding risk to determine appropriate therapy and management.

B. Stratification of patients.

Table 17: Stroke risk using the CHADS2 score

C	Congestive Heart Failure	1 point
H	Hypertension	1 point
A	Age (> 75 years)	1 point
D	Diabetes mellitus	1 point
S	Prior Stroke or TIA	2 points

Table 18: $CHADS_2$ Adjusted Stroke Rate without Anticoagulation

$CHADS_2$ Score	**Adjusted stroke rate without anticoagulation, %/yr (95% CI)**
0	1.9 (1.2 – 3.0)
1	2.8 (2.0 – 3.8)
2	4.0 (3.1 – 5.1)
3	5.9 (4.6 – 7.3)
4	8.5 (6.3 – 11.1)
5	12.5 (8.2 – 17.5)
6	18.2 (10.5 – 27.4)

Table 19: Stroke risk using the CHADS2-VASc score:

C	CHF or LVEF $\leq$ 40%	1 point
H	Hypertension	1 point
A	Age (> 75 years)	2 points
D	Diabetes mellitus prior	1 point
S	Stroke or TIA or thromboembolism	2 points
V	Vascular disease (prior MI, peripheral artery disease, or aortic plaque)	1 point
A	Age 65-74 years	1 point
Sc	Sex category (female)	1 point

Table 20: CHADS2VASc Score Adjusted Stroke Rate per Year

VASc Score	**Adjusted stroke rate, %/yr**
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

Table 21: Major bleeding risk using the HAS-BLED score

H	Hypertension	1 point
A	Abnormal renal or hepatic function	1 point each
S	Stroke	1 point
B	Bleeding	1 point
L	Labile INRs	1 point
E	Elderly (age > 65 years)	1 point
D	Drug or alcohol	1 point each

Recommendations[53]:

- § CHADS2 ≥ 2 → Oral anticoagulant
- § CHADS2 = 0 or 1→ calculate CHA2DS2-VASc
- § CHA2DS2-VASc is recommended if CHADS2≤ 1
- § CHA2DS2-VASc = 0→ No antithrombotic therapy
- § CHA2DS2-VASc = 1→ Oral anticoagulant or ASA, oral anticoagulant preferred
- § CHA2DS2-VASc ≥ 2 → Oral anticoagulant. Vigilance is required in patients with high risk of major bleeds (HAS-BLED≥ 3). Closer monitoring and follow up is warranted in this population.
- § Aspirin (≥ 80 mg) is effective but not as effective as warfarin.

Table 22: HAS-BLED Score and Major Bleeds Risk

HAS-BLED Score	Major Bleeds (%/year)
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.5

C. Choice of oral anticoagulant

- § Currently, the oral vitamin K antagonist, warfarin, is the most widely used.
- § An alternative vitamin K antagonist is nicoumalone , for patients allergic to warfarin.
- § **Maintain an INR of 2.0-3.0** with vitamin K antagonists to prevent embolic stroke.
- § Patients with chronic atrial fibrillation of unknown duration, in the absence of an acute embolic event, do not require heparin therapy during the initiation of warfarin therapy.
- § Dabigatran, an oral direct thrombin inhibitor, and rivaroxaban, an oral factor Xa inhibitor, are new alternatives to vitamin K antagonists.
- § Both dabigatran and rivaroxaban are as efficacious as warfarin in preventing stroke, with lower risk of intracranial bleeding. However, they are excreted primarily by the kidney, antidotes are very expensive, and are not readily monitored with standard laboratory tests[53].

D. Atrial Fibrillation following open heart surgery

- § Warfarin is recommended for 3 months following open heart surgery, provided the patient reverts to normal sinus rhythm.

E. Cardioversion of Atrial Fibrillation

- § For AF < 48 hours, anticoagulation is not required prior to cardioversion
- § For AF >48 hours (or of unknown duration), warfarin is recommended for 3 weeks before and at least 4 weeks after successful cardioversion.
- § The duration of warfarin therapy, regardless of cardioversion outcome, will be decided by the treating cardiologist.

Bridging Therapy

Bridging Therapy is defined as the administration of a short-acting anticoagulant, consisting of subcutaneous LMWH or IV UFH, for a 10- to 12-day period during interruption of VKA therapy when the international normalized ratio (INR) is not within a therapeutic range[54].

A. Peri-operative Management of Anticoagulation

- § Indications for bridging therapy:
- § Patients on warfarin therapy for atrial fibrillation, venous thromboembolism (VTE) or mechanical heart valves who are at **high or moderate risk** of developing thromboembolism.

Table 23: Risk Assessment for Development of VTE

Risk	AF	VTE	Mechanical heart valve
High	CHADS2 = 5 or 6 CVA or TIA within the past 3 months Rheumatic valvular heart disease	VTE within the past 3 months Severe thrombophilia (e.g. deficiency in proteins C, S or antithrombin, antiphospholipid antibodies)	Mitral valve prosthesis Older aortic valve prosthesis CVA or TIA within the past 6 months
Moderate	$CHADS_2$ = 3 or 4	VTE within the past 3 to 12 months Recurrent VTE Active cancer (treated within 6 months or palliative)	Bileaflet aortic valve prosthesis and one of the following risk factors: - AF - Prior CVA or TIA - Hypertension - Diabetes - CHF - Age > 75 years
Low	CHADS2 = 0 to 2, with no prior CVA or TIA	VTE > 12 months ago, single episode, no other risk factors	Bi-leaflet aortic valve prosthesis with none of the above risk factors

Bridging Therapy

A. Recommended bridging therapy (not needed in low risk patients)[54]:

- § Discontinue warfarin 3 – 5 days before the surgery and commence LMWH (enoxaparin at 1.5mg/kg/day from 3 days pre-op (give 0.75mg/kg 1 day before the surgery).
- § Recommence warfarin at the regular dose 12 to 24 h after surgery (evening of or next morning).
- § *For high bleeding risk operative procedures, recommence enoxaparin at prophylactic dose of 40mg daily or 0.5mg/kg/day a day after the surgery.
- § For low bleeding risk procedures, recommence enoxaparin at 1.5mg/kg/day a day after the surgery.

*High bleeding risk operative procedures e.g. major orthopedic surgery, genitourinary surgery, neurosurgery, vascular surgery, endoscopy with possibility of biopsy, and abdominal hysterectomy

Note:

- § LMWH is NOT to be given within 24 hours of a surgical procedure.
- § For high risk surgeries (e.g. neurosurgery) or surgeries associated with a high incidence of bleeding (e.g. Urologic procedures), it is suggested that the pre- surgical LMWH dose on Day -1 and/or the post-operative doses of LMWH be omitted.
- § The pre-operative LMWH dose on Day-1 should not be given prior to neuraxial anaesthesia.

B. Surgical procedures in patients with renal impairment

- § Patients with moderate renal impairment (CrCl 15-30 mL/min) should receive only prophylactic doses of LMWH for bridging.
- § Patients with severe renal impairment (CrCl <15 mL/min) should receive Intravenous unfractionated heparin for bridging.

Table 24: Surgical Procedures in Patients on Dabigatran

CrCl, (ml/min)	Half-life (hours)	Timing of procedure after last dose of dabigatran	Timing of resumption of d abigatran after surgery (depends on procedure)
>80	13	2 days	The evening on the day after surgery
<50 – 80	15	2 days	As above
30 – 50	18	4 days	As above

C. Surgical procedures that do not necessarily require interruption of warfarin therapy[55]

1) Dental procedures: Simple dental procedures can be performed as long as the INR <3.0. Very complex procedures may require the perioperative bridging protocol.
2) Endoscopies without polypectomy or biopsy
3) Cystoscopies without biopsies
4) Cataract surgery

Acknowledgement:

We acknowledge the support of Bayer Pharmaceuticals and Sanofi towards the production of this guideline. We declare that neither Bayer nor Sanofi participated in the drafting of the guidelines or influenced the recommendations.

We also acknowledge the support of the International Society on Thrombosis and Haemostasis in reviewing this guideline.

Guideline Writing Committee

Awodu *OA MB;ChB, FMCPath, (COMMITTEE CHAIR)*
Professor of Haematology/Consultant Haematologist
University of Benin, Benin City, Edo State, Nigeria

Shokunbi *WA MB; BS FMCPath, FWACP (lab Med), FAS*
Professor of Haematology/Consultant Haematologist
College of Medicine, University of Ibadan, Oyo State, Nigeria

Akanmu A Sulaimon *MB; BS FMCPath*
Professor of Haematology and Blood Transfusion/ Consutant
Haematologist College of Medicine, University of Lagos, Lagos, Nigeria

Ogbe O Patrick *MB; BS /, FWACP (lab Med)*
Chief Consultant Haematologist, National Hospital, Abuja, Nigeria

Bolarinwa Rahman *MB;ChB, FMCPath*
Senior Lecturer/Consultant Haematologist,
Obafemi Awolowo University, Ile Ife

Yuguda Saleh *MB; BS, FMCPath*
Lecturer/Consultant Haematologist
Dept of Haematology, Gombe State University/Federal Teaching
Hospital, Gombe, Gombe State, Nigeria

Omunakwe *H MB; BS, DOccMed, FMCPath*
Consultant Haematologist
Braithwaite Memorial Specialist Hospital, Port Harcourt

Okoye Helen *C MB; BS, FMCPath, FWACP (Lab Med)*
Lecturer/Consultant Haematologist
University of Nigeria, Enugu

REFERENCES

1. Shokunbi WA, Durosinmi MA, Aken'Ova YA, Olatunji OO, Akanmu AS, Wakama TT, *et al*..Lymphoma Treatment Guidelines for Nigeria. Nigerian Society for Haematology and Blood Transfusion.2012
2. Adeyemo TA, Adediran A, Akinbami AA, Akanmu AS. Prevalence of activated protein C resistance (Factor V Leiden) in Lagos, Nigeria. *Niger J. Clin Pract*. 2012; 15(2):136-4
3. Ajibola SO, Adeyemo TA, Afolabi BB, Akanmu AS. Utility of a single mid-trimester measurement of plasminogen activator Type 1 and fibronectin to predict preeclampsia in pregnancy. *Niger Med J*. 2016; 57(4):213–6.
4. Tyler W Buckner, Nigel S Key. Venous Thrombosis in Blacks. *Circulation*. 2012; 125(6):837–9.
5. Roberts LN, Patel RK, Arya R. Venous thromboembolism and ethnicity. *Br J Haematol*. 2009; 146(4):369–83.
6. Patel RK, Roopen A. Venous thrombo-embolism: racial and ethnic influences. *Therapy*. 2008; 5(2):169–75.
7. Sotunmbi PT, Idowu AT, Akang EEU, Aken'Ova YA. Prevalence of venous thromboembolism at post-mortem in an African population: a cause for concern. *Afr J Med med Sci.* 2006; 35(3):345–8.
8. Okunade MA, Kotila TR, Shokunbi WA, Aken'Ova YA. Venous thromboembolism in Ibadan: A five year experience (1986-1990). *Niger Q J Hosp Med*. 1998; 8(2):80–2.
9. T R Kotila, F A Fasola, E O Busari A revisit of venous thromboembolism. *Afri J Med med Sci.* 2013; 42 (2): 177-81
10. Fatai O. Bello; Sulaimon Akanmu; Titilope Adeyemo; Funmi Lesi; Prosper Okonkwo; Sade Ogunsola; Phyllis Kanki Derangement in Protein S and C4b binding protein levels in HIV infected adults. In CROI 2016 Abstract 281 Boston, USA;
11. Ahmed SG, Tahir A, Hassan AW, Kyari O, Ibrahim UA. Clinical Risk factors for deep vein thrombosis in Maiduguri - Nigeria. *Highl Med Res J*. 2003; 1(4):9–16.
12. Fall AO, Proulle V, Sall A, Mbaye A, Ba PS, Diao M, et al. Risk Factors for Thrombosis in an African Population. *Clin Med Insights Blood Disord*. 2014; 7:1–6.
13. Narani KK. Deep vein thrombosis and pulmonary embolism – Prevention, management, and anaesthetic considerations. *Indian J Anaesth*. 2010; 54(1):8–17.
14. Kaushansky K, Lichtman M, Beutler E, Kipps T, Prchal J, Seligsohn U. Williams Hematology, Eighth Edition. 8 edition. New York: McGraw-Hill Education / Medical; 2010. 2460.
15. Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, *et al*. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *The Lancet*. 1997; 350(9094):1795–8.
16. American Academy of Family Physicians/ American College of Physicians. Panel on Deep Venous Thrombosis/Pulmonary Embolism. Current Diagnosis of Venous Thromboembolism in Primary Care: A Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Intern Med*. 2007; 146:454–458.
17. Wells P, Anderson D. The diagnosis and treatment of venous thromboembolism. ASH Educ Program Book. 2013 (1):457–63.
18. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, *et al*. Evaluation of D-Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis. *N Engl J Med*. 2003; 349 (13):1227–35.
19. Huisman MV, Klok FA. Current challenges in diagnostic imaging of venous thromboembolism. *Blood*. 2015; 126(21): 2376–82.
20. Makris M. Thrombophilia: grading the risk. Blood. 2009; 113(21):5038–9.
21. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, *et al*. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016; 149(2):315–52.
22. Venous thromboembolism in over 16S: reducing the risk for hospital-acquired deep

venous thrombosis and pulmonary embolism patients in hospital | *Guidance and guidelines|NICE* [internet]. [cited May 27, 2018. Available from: hps://www.nice.org.uk/guidance (NG 89). March 2018

23. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ, American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141(2):7S–47S.

24. Hull RD, Raskob GE, Hirsh J, Jay RM, Leclerc JR, Geerts WH, *et al*. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. *N Engl J Med*. 1986; 315(18):1109–14.

25. Prandoni P, Carnovali M, Marchiori A, Galilei Investigators. Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism. *Arch Intern Med*. 2004; 164(10):1077–83.

26. Kearon C, Ginsberg JS, Julian JA, Douketis J, Solymoss S, Ockelford P, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA*. 2006; 296(8):935–42.

27. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a 'standard care' nomogram. A randomized controlled trial. *Ann Intern Med*. 1993; 119(9):874–81.

28. Smythe MA, Priziola J, Dobesh PP, Wirth D, Cuker A, Wittkowsky AK. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. *J Thromb Thrombolysis*. 2016 Jan; 41(1):165–86.

29. van Veen JJ, Maclean RM, Hampton KK, Laidlaw S, Kitchen S, Toth P, *et al*. Protamine reversal of low molecular weight heparin: clinically effective? Blood Coagul Fibrinolysis *Int J Haemost Thromb*. 2011; 22(7):565–70.

30. Akanmu A. S. Nnodu O. E. Giwa S.O Salako L. A. Akinsete I. Adebule G. T. Adekoya- Cole T. O. Odunubi O.O. Efficacy & Safety of Enoxaparin, A low molecular weight heparin In the Prevention of Deep Vein in Nigerian patients After Orthopaedic Surgery. *Afr J Med med Sci*. 2004. 33,335-350.

31. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141(2 Suppl):e24S–e43S.

32. Witt DM, Clark NP, Kaatz S, Schnurr T, Ansell JE. Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. *J Thromb Thrombolysis*. 2016; 41(1):187–205.

33. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost* . 2014; 12(3):320–8.

34. Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis*. 2016; 41(1):206–32.

35. Garcia D, Libby E, Crowther MA. The new oral anticoagulants. *Blood*. 2010; 115(1):15–20.

36. Anticoagulation Guidelines of the RUSH University Medical Centre, Chicago, Illinois. RUSH University Medical Centre, Chicago, Illinois; 2014.

37. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos Biol Fate Chem*. 2008; 36(2):386–99.

38. Vedantham S, Piazza G, Sista AK, Goldenberg NA. Guidance for the use of thrombolytic therapy for the treatment of venous thromboembolism. *J Thromb Thrombolysis*. 2016; 41(1):68–80.

39. Ali MR, Salim Hossain M, Islam MA, Saiful Islam Arman M, Sarwar Raju G, Dasgupta P, *et. al.* Aspect of thrombolytic therapy: a

review. *Scientific World Journal*. 2014; 2014:586510.

40. DeYoung E, Minocha J. Inferior Vena Cava Filters: Guidelines, Best Practice, and Expanding Indications. *Semin Interv Radiol*. 2016; 33(2):65–70.

41. Vanek VW. Meta-analysis of effectiveness of intermittent pneumatic compression devices with a comparison of thigh-high to knee-high sleeves. *Am Surg*. 1998; 64(11):1050-8

42. Murphy O, O'Connell O, Liston R, Connaughton J, Costello R, Breiden J, *et al*. Venous thromboembolism risk and prophylaxis in the acute hospital care setting: the Irish results of the ENDORSE study. *Ir Med J*. 2012; 105(5):140–3.

43. Cohen AT, Tapson VF, Bergmann J-F, Goldhaber SZ, Kakkar AK, Deslandes B, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *The Lancet*. 2008; 371 (9610):387–94.

44. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, *et al*. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141(2 Suppl):e227S–e277S.

45. David P, David W, Jenniefr RE, David G, Mohammed MK, Alok AK, *et al.* Handbook of Thromboprophylaxis. 3rd edition. Springer Internation Publishing Switzerland; 2016.

46. Jørgensen PS, Warming T, Hansen K, Paltved C, Vibeke Berg H, Jensen R, *et al*. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study. *Thromb Res*. 2002; 105(6):477–80.

47. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, *et al*. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008; 133 (6:381S–453S).

48. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J *Thromb Haemost*. 2007; 5(3):632–4.

49. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood.* 2008; 111(10):4902–7.

50. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, *et al.* Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia.* 2008; 22(2):414–23.

51. Bullano MF, Willey V, Hauch O, Wygant G, Spyropoulos AC, Hoffman L. Longitudinal evaluation of health plan cost per venous thromboembolism or bleed event in patients with a prior venous thromboembolism event during hospitalization. *J Manag Care Pharm*. 2005; 11(8):663–73.

52. Lyman GH, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, *et al.* Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013; 31(17):2189–204.

53. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos A-M, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012; 141(2 Suppl):e691S–e736S.

54. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, *et al.* Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012; 141(2 Suppl): e531S–e575S.

55. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, *et al.* Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012; 141(2 Suppl):e326S–e350S.

ISSN 263530240-5